Risk factors for the development of epilepsy in patients with brain metastasis

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Abstract: BACKGROUND Current guidelines do not recommend primary prophylactic anti-epileptic drug therapy for patients with brain metastases (BM). Yet, subgroups of patients at high seizure risk might still benefit from prophylaxis. METHODS We identified 799 patients diagnosed with BM by retrospective screening of our electronic chart system. Candidate risk factors for the development of epilepsy were tested by univariate and multivariate Cox regression models. RESULTS Epilepsy was diagnosed in 226 of 799 patients (28%). Risk factors for epilepsy in non-operated patients were single BM (p=0.002, hazard ratio (HR) 3.2, 95% confidence interval (CI) 1.5-6.6) and detection of tumoral hemorrhage (p= 0.008, HR 2.5, 95% CI 1.3-4.9). Pre-operative seizures occurred predominantly in patients with supratentorial BM (p=0.003, HR 20.78, 95% CI 2.8-153.4) and lung cancer (p= 0.022; HR 2.0, 95% CI 1.1-3.6). Post-operative seizures were associated with supratentorial localization (p=0.017, HR 5.8, 95% CI 1.4-24.3), incomplete resection (p=0.005, HR 4.6, 95% CI 1.6-13.1), and by trend for multiple brain surgeries (p=0.095, HR 1.9, 95%CI 0.9-4.0). These risk factors were integrated into a predictive score model for post-operative epilepsy (score sum 0-8). A gradual increase of seizure rates along with higher sum score was confirmed post-hoc (score 0, no seizures; score 8, 48% seizures). Receiver-operating characteristic analysis supported diagnostic accuracy (p=0.00001, AUC=0.75). CONCLUSIONS Here we have defined risk profiles for the development of BM-related epilepsy and derived a score which might help to estimate the risk of post-operative seizures and identify individuals at risk who might benefit from primary prophylactic anti-epileptic drug therapy.

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Short title: Epilepsy in patients with brain metastasis

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Abstract

BACKGROUND: Current guidelines do not recommend primary prophylactic anti-epileptic drug therapy for patients with brain metastases (BM). Yet, subgroups of patients at high seizure risk might still benefit from prophylaxis.

METHODS: We identified 799 patients diagnosed with BM by retrospective screening of our electronic chart system. Candidate risk factors for the development of epilepsy were tested by univariate and multivariate Cox regression models.

RESULTS: Epilepsy was diagnosed in 226 of 799 patients (28%). Risk factors for epilepsy in non-operated patients were single BM (p=0.002, hazard ratio (HR) 3.2, 95% confidence interval (CI) 1.5-6.6) and detection of tumoral hemorrhage (p= 0.008, HR 2.5, 95% CI 1.3-4.9). Pre-operative seizures occurred predominantly in patients with supratentorial BM (p=0.003, HR 20.78, 95% CI 2.8-153.4) and lung cancer (p= 0.022; HR 2.0, 95% CI 1.1-3.6). Post-operative seizures were associated with supratentorial localization (p=0.017, HR 5.8, 95% CI 1.4-24.3), incomplete resection (p=0.005, HR 4.6, 95% CI 1.6-13.1), and by trend for multiple brain surgeries (p=0.095, HR 1.9, 95%CI 0.9-4.0). These risk factors were integrated into a predictive score model for post-operative epilepsy (score sum 0-8). A gradual increase of seizure rates along with higher sum score was confirmed post-hoc (score 0, no seizures; score 8, 48% seizures). Receiver-operating characteristic analysis supported diagnostic accuracy (p=0.00001, AUC=0.75).

CONCLUSIONS: Here we have defined risk profiles for the development of BM-related epilepsy and derived a score which might help to estimate the risk of post-operative seizures and identify individuals at risk who might benefit from primary prophylactic anti-epileptic drug therapy.

Key points

- Epilepsy was diagnosed in 226 of 799 patients (28%) with brain metastasis (BM)
- Post-operative seizures were associated with supratentorial BM, residual tumor or repeat brain surgery
- A predictive model for seizures was derived from patients` risk profiles

Importance of the study

Brain tumor-related epilepsy is a frequent and clinically highly relevant complication of brain metastasis. However, current guidelines do not recommend primary prophylactic antiepileptic drug (AED) treatment for seizure-free patients with brain metastasis since no benefit from general prophylaxis has been demonstrated so far. Furthermore, AED treatment may have significant side effects, interfere with systemic cancer therapy, and generates addditional cost. Conversely, seizure prevention is of high clinical importance since seizures negatively impact quality of life, for patients and for caregivers, and possibly outcome, too. In clinical practice, AED treatment is started following a first seizure, or based on an individual decision of the treating physician. Here we provide risk profiles for the development of seizures in patients with and without tumor resection. We have developed a predictive score to support clinicians in the identification of patients at high risk for post-operative epileptic seizures who might benefit from primary prophylaxis with AED.

Keywords: seizure, prevention, prophylaxis, CNS, score

Introduction

Brain tumor-related epilepsy (BTRE) is common in patients with brain metastases (BM) from systemic tumors and thought to contribute to morbidity and mortality [1,2]. Freedom from seizures is essential for favorable quality of life in brain tumor patients [3-5]. BTRE life-time risk in BM patients is estimated at 20-35% to 67% [6-8]. Diagnosis of BTRE commonly necessitates the initiation of secondary prophylaxis whereas primary prophylactic AED treatment in response to a BM diagnosis is not indicated [9]. This is because several retrospective studies have failed to demonstrate a general risk reduction for developing BTRE with primary prophylaxis [10-12]. However, subgroups of patients with high risk of seizures might still benefit from primary prophylaxis [13].

There are only limited data to estimate the risk of developing BTRE in BM patients, mostly from retrospective studies of patient cohorts that also include patients with primary brain tumors [7,14] or patients with distinct tumor entities, e.g. melanoma [13]. Although available data and current guidelines [9] do not support the concept of primary prophylaxis with AED, although these are nevertheless often prescribed in BM patients without BTRE, e.g., prior to BM resection or on an individual base if the patient is thought to be at increased seizure risk. Possible seizure prevention has to be weighed against risk of drug interactions and of relevant side effects associated with AED therapy. This is particularly true for older AED like phenytoin or phenobarbital [15].

A better understanding of risk factors for BTRE might help to define a role for primary prophylactic AED therapy in subgroups of BM patients. Gross total resection, radiotherapy and chemotherapy are thought to contribute to seizure control in glioma patients [7,8,17]. Conversely, pre- or post-operative hemorrhage and multiple lesions

were associated with increased seizure risk in BM patients [13] and detection of cortical hemosiderin correlated with seizure risk in a retrospective study including 36 BM patients [14].

The major goal of this study was to define subgroups of BM patients at high risk for BTRE that might benefit from primary AED therapy. To this end, we retrospectively studied a clinically well-annotated cohort of 811 patients with BM. Since surgery can either contribute to improved seizure control following resection or can in turn result in post-operative onset of new seizures, separate analyses for pre-operative BTRE, post-operative BTRE, and BTRE in non-operated patients were conducted, with the intent to build risk prediction models for BTRE in BM patients.

Materials and methods

Patients

We screened the electronic chart system of the University Hospital Zurich for patients diagnosed with BM between January 2004 and December 2014, employing the search term “brain metastasis”. Of 843 adult patients, 13 patients were excluded because of missing informed consent and 19 patients because of alternative diagnoses. Of the remaining 811 patients, 568 patients had a brain biopsy or resection. Follow-up data until death were available for 628 patients (77%) whereas 183 patients (23%) were followed up for a median of 17.0 months (95% CI 12.0-23.0 months). This study was approved by the Cantonal Ethics Committee Zurich (KEK-ZH-Nr. 2018-00192).

Assessments

At least one unprovoked seizure in a patient with a diagnosis of BM was defined as BTRE according to the criteria of the International League Against Epilepsy (ILAE) that were valid when data were collected [18]. A new classification of seizures have been established meanwhile [19]. Post-operative epilepsy was diagnosed in patients with documented epileptic seizures during post-operative follow-up, except for seizures within 7 days of craniotomy. The latter are referred to as acute symptomatic post-operative and thus provoked seizures [20]. All patients with provoked seizures only were assigned to the non-BTRE group.

Patient characteristics, histopathological data and clinical data including neurological deficits, seizure history, post-operative course, complications and medication were obtained by electronic chart reviews. Reports of cranial computed tomography (CT)

and magnetic resonance imaging (MRI) scans were reviewed to assess number, localization and morphology of BM and to define presence of tumoral hemorrhage, tumor progression and extent of resection. Absence of contrast-enhancing tumor on post-operative MRI scans was rated as gross total resection.

Statistical methods

Analysis of nominal variables was performed employing the Chi-square test, analysis of linearly scaled variables was done with the Mann-Whitney U test. Significant differences of paired nominal data were assessed employing McNemar's test. Differences between ordinally coded data in unpaired samples were assessed by the Kruskal-Wallis test. Binary logistic regression analysis was performed to assess for factors independently associated with pre-operative seizures. Variables which were associated with BTRE in univariate analyses were carried forward for multivariate testing using a Cox regression model including post-operative follow-up for seizures and seizure occurrence. Other variables previously reported to be associated with seizures were included in our model as possible confounders. Multivariate models for BTRE were derived separately for operated and non-operated patients, based on results from univariate analysis. We integrated the results in a predictive score model. Score values were derived from respective hazard ratios (HR) for each item and confirmed using beta-coefficient values of regression. Receiver-operating characteristic (ROC) curves were used to rate score validity. An area under the curve (AUC) of 0.5 reflects no discrimination between risk groups, an AUC of 1 a perfect discrimination between subjects at high and low risk, and an AUC>0.7 is widely accepted as cut-off for clinically relevant discrimination capacity of a clinical score [21].

Statistical analysis was performed by IBM SPSS statistics ®, Version 23 (IBM Co., Armonk, NY, USA) and GraphPad Prism software, version 7.0 (La Jolla, CA, USA). For two-sided p-values, results with $p<0.05$ were considered significant and with $p<0.01$ highly significant.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request (fabian.wolpert@usz.ch).

Results

Patient characteristics

Interrogation of the electronic database allowed the identification of 811 BM patients. Twelve patients were excluded because of a history of prior epilepsy (Figure 1, CONSORT chart). Of the final cohort of 799 patients, 237 patients (30%) had at least one documented seizure. In five patients, a provocation factor, e.g., more than moderate alcohol consumption, alcohol withdrawal, low serum sodium levels or infection, was reported, two of these five patients later suffered from at least one unprovoked seizure and then fulfilled ILAE criteria for BTRE. Ten patients had a seizure within the first week after surgery which were rated as provoked by surgery [18]. Two of these patients had at least one or more unprovoked seizures in the further course of disease and were therefore included in the BTRE group. Altogether, 226 of 799 patients (28%) had at least one unprovoked epileptic seizure and thus fulfilled BTRE criteria (Table 1). Seizure rates varied from one up to 13 seizures (Figure 2A). There was no association between the first clinical symptom of BM and BTRE (Figure 2B). Most seizures occurred within one week from diagnosis of BM whereas other seizures occurred preferentially in the later course of disease beyond 12 weeks, potentially indicative of progressive disease (Figure 2C). In operated patients the majority of the first and second seizures occurred before surgery whereas few seizures occurred within the first 12 weeks after surgery (Figure 2D), consistent with surgery-afforded seizure control.

To further assess the role of tumor progression for BTRE in patients with known brain metastasis, we evaluated imaging results obtained within one week of the first

seizure. This information was available for 76 previously seizure-free patients. Tumor progression was noted in 47 of these patients (62%).

AED use in BTRE

AED treatment was assessed before and after the time of occurrence of a first seizure as well as one year after the diagnosis of BM. Information on AED prophylaxis after diagnosis of BM and prior to any documented seizure was available for 796 patients (Table S1). BTRE risk did not differ between patients with (31%) *versus* without primary prophylaxis (31%) (Table 1). Justification of primary prophylaxis was documented for 138 of 153 patients: individual decisions of treating clinicians (52 patients, 38%), pathologic EEG findings (30 patients, 22%), continuation of peri-operative prophylaxis (52 patients, 38%), other reasons like treatment of neuropathic pain (4 patients, 3%). Information on AED prophylaxis was available for 554 of 557 operated patients, in 115 of those BTRE was diagnosed before surgery. In the remaining patients, BTRE was diagnosed in 14 of 236 patients (5.9%) with no AED prophylaxis, in 32 of 138 patients (23.2%) with primary prophylaxis and 1 of 65 patients (1.5%) with peri-operative prophylaxis which was started prior to and stopped within 4 weeks after surgery (p=0.0005).

Seizure types

There was a trend towards association of generalized non-convulsive seizures with lower median KPS (p=0.053) and with higher number of BM (p=0.073, Kruskal-Wallis test). There was no association of seizure type and gender (p=0.187), extent of resection (p=0.121), initial symptom (p=0.405), lobe (p=0.312), hemisphere (p=0.593) or detection of intracranial hemorrhage (p=0.555) (Chi-square test). Focal

seizures with retained awareness were more common in operated patients (75 of 182 patients, 41.2% *versus* 10 of 47 patients, 21.3% in non-operated patients) whereas focal seizures with impaired awareness occurred more frequently in non-operated patients (11 of 47 patients, 23.4% *versus* 11 of 182 patients, 6.0%, in operated patients; p=0.002) (Chi-square test).

Risk factors for BTRE in non-operated patients

Characteristics of 242 patients, who were not operated, are shown in Table S2; 49 patients (20.2%) had BTRE. BTRE was associated with number of BM (p=0.013, Mann-Whitney U test) and more common in patients with one BM (17 of 51 patients, 33.3%) than in patients with multiple BM (31 of 189 patients, 16.5%; p=0.007, Chi-square test). Patients with a single cortical supratentorial BM, defined as less than one cm distance from the cortex, or subcortical BM, defined as 1-2 cm from the cortex, showed no difference in BTRE rate, compared with BM in the deep white matter (> 2 cm from the cortex; Table S2). There was no association of BTRE with histology of the primary tumor (p=0.816), chemotherapy after diagnosis of BM (p=0.911, data not shown) or steroid intake at any time during the clinical course (p=0.977, data not shown, all Chi-square test). Supratentorial *versus* infratentorial tumor location of a single BM was not associated with BTRE either. This difference was still not significant for early occurrence of BTRE (< 12 weeks; supratentorial: 6 of 24 patients (25.0%) compared to infratentorial: 1 of 9 patients (11.1%), p=0.360). Hemorrhagic transformation of the tumor was found upon initial imaging in more than a third of the patients, with the highest rate in melanoma. Detection of tumoral hemorrhage was associated with the diagnosis of BTRE (p=0.021). We used a Cox regression model with time to first seizure as an outcome measure for multivariate

testing to exclude bias from diverging survival. Both single BM (p=0.002, HR 3.2, 95% CI 1.5-6.6) and detection of tumoral hemorrhage (p=0.008, HR 2.5, 95% CI 1.3-4.9) were retained as independent factors associated with BTRE. Post-hoc calculation revealed BTRE in 13 of 116 patients (11.2%) with none, in 27 of 106 patients (25.5%) with one and in 7 of 14 patients (50%) with both risk factors, single BM and tumoral hemorrhage.

Risk factors for pre-operative seizures

Information on pre-operative seizures was available for 554 of 557 operated patients. They were reported in 112 of these patients (19.2%) and were the first symptom of BM in 62 of these patients (11.2%). There was no association between pre-operative BTRE and the number of metastases (p=0.433), KPS (p=0.319), age (p=0.160, Table S3), or steroid use (p=0.187, not shown) or initial symptom (p=0.572, both Chi-square test). However, there was an association between primary tumor histology and pre-operative seizures (p=0.037): we noted an increased incidence of pre-operative seizures in patients with lung cancer (p=0.007) and a decreased incidence of pre-operative seizures in patients with breast cancer (p=0.005). Furthermore, patients with a single cortical or sub-cortical supratentorial BM showed a trend towards increased seizure risk compared to deep-seated BM (p=0.075). The largest fraction of patients with pre-operative seizures had frontal BM (33.7%, p=0.007), followed by parietal single BM (24.4%, p=0.911), occipital (16.0%, p=0.297) and temporal (6.1%, p=0.11) single BM (Table S3).

Supratentorial *versus* infratentorial localization was the key risk factor for pre-operative seizures on multivariate analysis (p=0.003, HR 20.78, 95% CI 2.8-153.4), followed by lung cancer as the primary tumor (p=0.022, HR 2.0, 95% CI 1.1-3.6). A

sub-analysis for supratentorial tumors revealed localization in the frontal lobe (p=0.001, HR 2.78, 95% CI 1.5-5.2) as an independent risk factor.

Risk factors for postoperative seizures

The associations of clinical disease characteristics with post-operative BTRE are summarized in Table 2. Supratentorial *versus* infratentorial (p=0.012), or occipital *versus* other locations (p=0.027) were associated with post-operative seizures. Furthermore, single *versus* more than one brain surgery in the disease course (p=0.00001), and cerebral venous thrombosis (p=0.030) were associated with post-operative BTRE. BTRE was less common in patients following gross total resection *versus* incomplete resection (p=0.008). The development of post-operative BTRE was associated with brain irradiation (p=0.013, Table 1) as well as chemotherapy (p=0.002, Table 1).

We then assessed the occurrence of seizures before and after surgery. Altogether, there was no significant association between pre- and post-operative seizure occurrence (p=0.077, McNemar test). There was also no significant association of pre- with postoperative seizures in the subgroup of 197 patients with only single supratentorial metastasis~~,~~ with a median follow-up of 6 months (95% CI 6.0-8.0 months) (Figure 3).

Next, we evaluated the association of extent of resection determined by post-operative imaging obtained within one week with postoperative BTRE in patients with single supratentorial BM. Risk of postoperative seizures was significantly higher after biopsy or partial resection than after gross total resection (p=0.008) (Table 2).

We then focused on patients with single supratentorial BM who had been seizure-free prior to surgery and explored an association of new BTRE with extent of

resection. Twenty of 66 patients (30.3%) who had a biopsy or partial resection developed post-operative BTRE, compared with only 2 of 38 patients (5.3%) with gross total resection (p=0.003, Chi-square test). In contrast to pre-operative seizures that were associated with frontal localization of single BM, new diagnosis of BTRE after surgery was associated with occipital tumor localization (p=0.027, Table 2). In contrast to pre-operative seizures, tumor histology was not associated with post-operative seizures (p=0.479).

Factors that were associated with post-operative seizures in univariate analysis were then tested in multivariate analysis, using a Cox regression model. Median post-operative follow-up for seizures was 6.0 months (95% CI 6.0-8.0). Supratentorial location (p=0.017, HR 5.8, 95% CI 1.4-24.3) and incomplete resection (p=0.005, HR 4.6, 95% CI 1.6-13.1) were independently associated with post-operative seizures, multiple surgeries (p=0.095, HR 1.9, 95% CI 0.9-4.0) were associated with increased rate of post-operative seizures by trend (Figure 4A).

Score models for prediction of post-operative seizures

Finally we integrated the factors associated with post-operative seizures into a model where supratentorial localization accounts for a score value of four, incomplete resection for a score of three and multiple surgeries for a score of one, based on HR values from multivariate analysis. ROC analysis supported the diagnostic accuracy of the score (p=0.000014, AUC=0.75, 95% CI 0.66-0.84) (Figure 4B). Post-hoc calculation of this score revealed a gradual increase in seizure frequency (Figure 4C).

Discussion

Although BTRE is a common complication in patients with BM, no general benefit from primary AED prophylaxis in BM patients has been demonstrated [9]. However, subgroups of BM patients might be at higher risk for BTRE and therefore benefit from primary prophylactic AED treatment, e.g., patients with BM from melanoma [13]. Here we define the risk profile for BTRE in a single institution cohort of 799 BM patients to identify subgroups of patients at increased risk of BTRE. We report a BTRE rate of 28%. The BTRE rate was lower in non-operated BM patients (20%) than in operated patients (32%) (Table 1). These data need to be interpreted with caution since the decision for surgery was likely often biased, e.g., to achieve seizure freedom or relief from intracranial pressure. Yet, because of this difference in BTRE frequency, we defined separate risk profiles for operated and non-operated patients. Since surgery has been reported to contribute to seizure control in patients with lower grade gliomas [22], we also decided to define separately the risk profile for pre-operative *versus* post-operative seizures. Non-operated patients with single BM had a higher BTRE rate than patients with multiple BM (Table S2). This finding was unexpected since a higher tumor burden should result in increased seizure risk. Yet, BM in potentially epileptogenic regions like the precentral gyrus or mesiotemporal region might often be difficult to resect. This would result in a selection bias towards non-operated patients with single lesions in highly epileptogenic regions whereas surgery is in general less frequently performed in patients with multiple BM, notable multiple small BM. We furthermore found an increased BTRE rate in non-operated patients with hemorrhagic lesions ($p=0.021$) [14], but no other clinical factors

considered to be potentially associated with BTRE, including depth of BM location, histology of the primary tumor, type of cancer treatment, or steroid intake.

In operated patients, supratentorial versus infratentorial localization was the key factor associated with pre-operative seizures on multivariate analysis (p=0.003, HR 20.8), followed by lung cancer as a primary tumor (p=0.022, HR 2.0). We next performed a subgroup analysis for patients with supratentorial tumors. Here, frontal localization was a risk factor for pre-operative seizures (p=0.001, HR 2.78). Primary AED prophylaxis was not associated with BTRE (p=0.582), however, patients who received peri-operative AED prophylaxis showed a significantly lower BTRE rate (p=0.0005). However, the latter finding has to be regarded with caution, since decisions for or against primary or peri-operative AED prophylaxis did not follow an algorithm, but were made on an individual basis.

A contribution of surgery to improved seizure control in BM patients with pre-operative BTRE is assumed, but remains unproven. We found no significant post-operative decrease of seizure rates in patients with pre-operative seizures, and inversely no increased rate of new seizures after surgery (Figure 3). However, seizure freedom is not the primary goal of BM surgery, and neurosurgical interventions are probably not planned accordingly. Epilepsy surgery with intra-operative EEG mapping for BM patients might be an interesting concept for individuals refractory to AED treatment.

When defining the risk profile for post-operative seizures, supratentorial *versus* infratentorial localization of a single metastasis was again a very strong predictor of new post-operative BTRE. We thus refined the seizure risk profile of supratentorial tumors. Univariate testing revealed incomplete resection (p=0.008), multiple

surgeries (p=0.0003) and occipital (p=0.027) localization, but not tumor histology (p=0.479) (Table 2) as possible predictors of higher seizure risk.

On multivariate analysis supratentorial localization (p=0.017, HR 5.8), incomplete resection (p=0.005, HR 4.6) and, by trend, multiple surgeries (p=0.095, HR 1.9) were retained as independent factors that were associated with post-operative seizures.

Our findings confirm and extend those from another recent cohort study [8]. Here, headache, cognitive deficits, multiple BM, and localization in the temporal or occipital lobe were reported as risk factors for pre-operative seizures, whereas absence of frontal lobe involvement and tumor size (diameter > 5 cm) were associated with poor pre-operative seizure control. We also found a lower frequency of post-operative seizures in patients with frontal BM, but no association with cognitive deficits or headache as first symptom from BM (Figure 2). Furthermore, we found no association between pre-operative seizures and the number of BM (Table S3). We confirm incomplete resection as a strong predictor of post-operative seizures [8]. In fact, we speculate that differential extent of resection may contribute to the relative association of post-operative BTRE with occipital rather than frontal BM location in our cohort. Alternatively, or in addition, there may be detection bias in pre-operative patients where motor seizures from frontal areas are more often recognized as such than more subtle seizure types, with occipital or parietal lesions. BM in the latter location may be more often diagnosed because of focal neuro(psycho)logical deficits.

The retrospective character of our cohort study is its major limitation. There was a possible bias on under-reporting of seizures. Sample sizes for some subgroup analyses were small. Causal links between BM and seizures are commonly considered compelling, but other seizure etiologies including metabolic disturbances

and side effects from cancer therapies are difficult to rule out, notably in a retrospective setting, and in this specific patient population.

A major strength is the overall large sample size which allowed us to define risk factors across treatment modalities or primary tumor entities. This contrasts with previous cohort studies or controlled trials that were e.g. restricted to tumor entities [13], single treatment modalities like neurosurgery [8,11] or included patients with primary brain tumors [7,14]. The size of our cohort allowed us also to perform some subgroup analyses and assess risk factors for seizures in different clinical settings, namely non-operated patients and operated individuals in the pre- and post-operative phase.

We finally developed a score model, by which groups with diverging post-operative seizure risk can be identified, ranging from 0% to almost 50%.

Although our score model is based on a retrospective analysis from a single center, it might provide a valuable clinical tool for clinical decision making. Patients who are not operated might not benefit from primary prophylaxis because of their low seizure risk, except for the subgroup with single and hemorrhagically transformed BM which showed a seizure rate of about 50%. Patients who are planned for surgery of a single supratentorial BM are candidates for peri-operative prophylaxis, which might be considered to be maintained in patients with incomplete resection of supratentorial single BM. Further validation in independent cohorts and ideally in prospective controlled trials is required to refine the outlined predictive model and to further improve its prognostic accuracy.

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Conflict of interest

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- MCN none declared
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Supplementary material

none

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13
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Figure legends

Figure 1: CONSORT chart. The consort chart shows the selection path for patients to be included this study. The upper part documents the preselection process to identify all BM patients and exclude patients with missing consent or alternative diagnosis. Next, patients with prior diagnosis of epilepsy were excluded from further assessment. The lower part shows separation of patients who underwent neurosurgery or no surgery. Pre- and post-operative BTRE risk profiles were assessed in separate.

Figure 2. Seizure characteristics in BM patients with BTRE. A. The documented numbers of seizures per number of patients are shown as bar plots. B. Stacked bar plots showing initial symptoms of patients with (grey) or without (black) seizures. Patients with a seizure as the first symptom of BM are excluded here. C,D. The occurrence of the first five seizures per number of patients over time is shown from the diagnosis of BM (C) or from surgery (D) as grouped bar plots.

Figure 3. Pre- and post-operative seizures in operated patients.
Schematic presentation of pre- and post-operative seizures in patients with a single superatentorial BM. Bold arrows indicate patients who had no diagnosis of BTRE and remained seizure free after surgery (upper bold arrow) or had a diagnosis of BTRE and ongoing seizures following surgery (lower bold arrow). Thin arrows indicate patients who were so far seizure free and develop post-operative BTRE (upper, down-going thin arrow) or patients with BTRE who become seizure free after surgery (lower up-going thin arrow). P-value as indicated (McNemar's test).

Figure 4. Predictive score model for post-operative BTRE. A. Results of multivariate testing are shown as a small table depicting risk factors, HR values with 95% CI and two-sided p-values. B. The ROC curve is shown for the predictive score model (dashed black line). AUC and p values as well as the 95% CI are indicated. C. The score sums and number of patients are shown as stacked bar plots. The black part of each bar represents the fraction of seizure-free patients, the grey part those with seizures. Percentages are indicated above each bar.

1

2

Figure 1

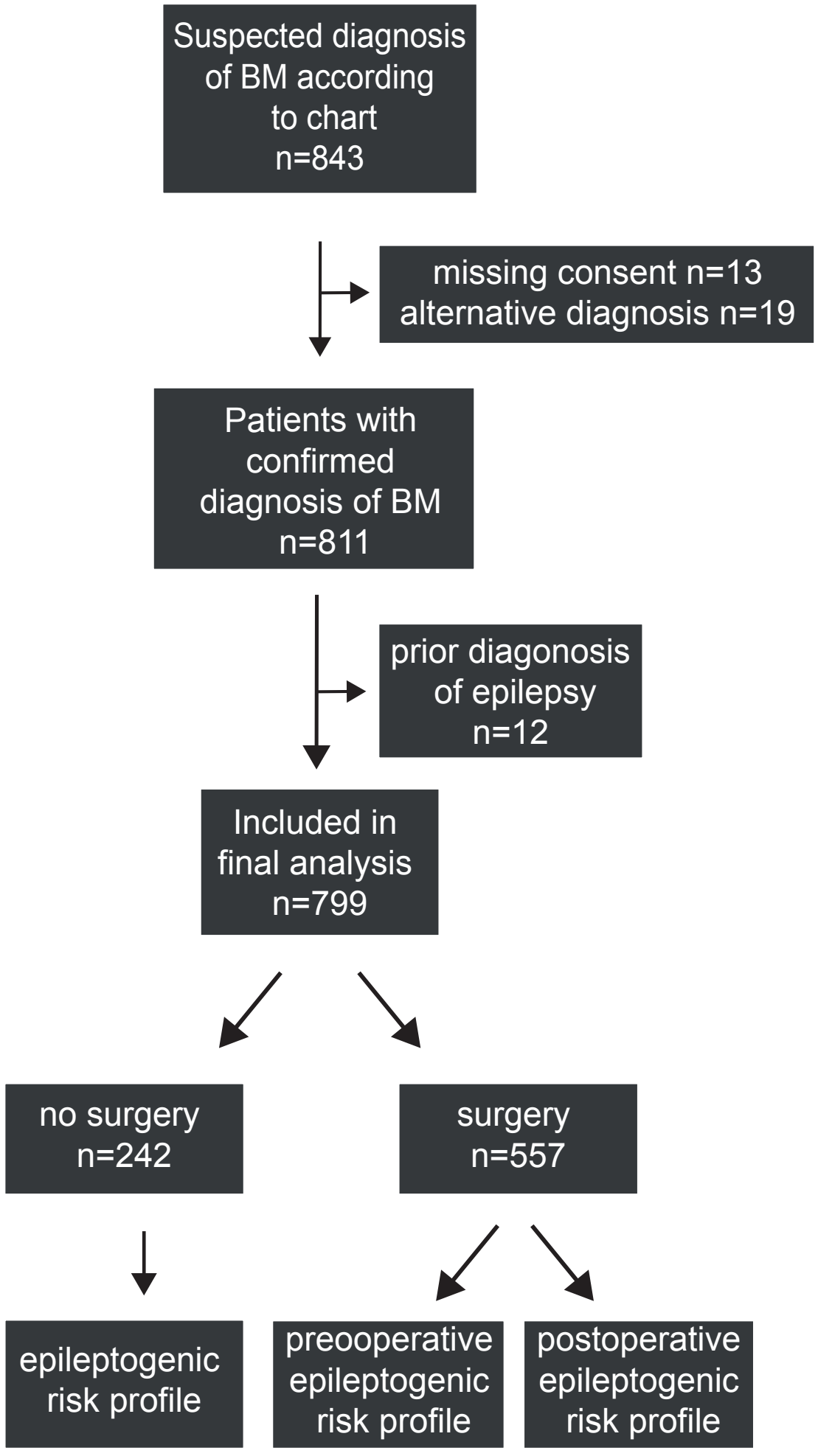

Suspected diagnosis of BM according to chart n=843
missing consent n=13
alternative diagnosis n=19
Patients with confirmed diagnosis of BM n=811
prior diagonosis of epilepsy n=12
Included in final analysis n=799
no surgery n=242
surgery n=557
epileptogenic risk profile
preooperative epileptogenic risk profile
postoperative epileptogenic risk profile

Figure 2

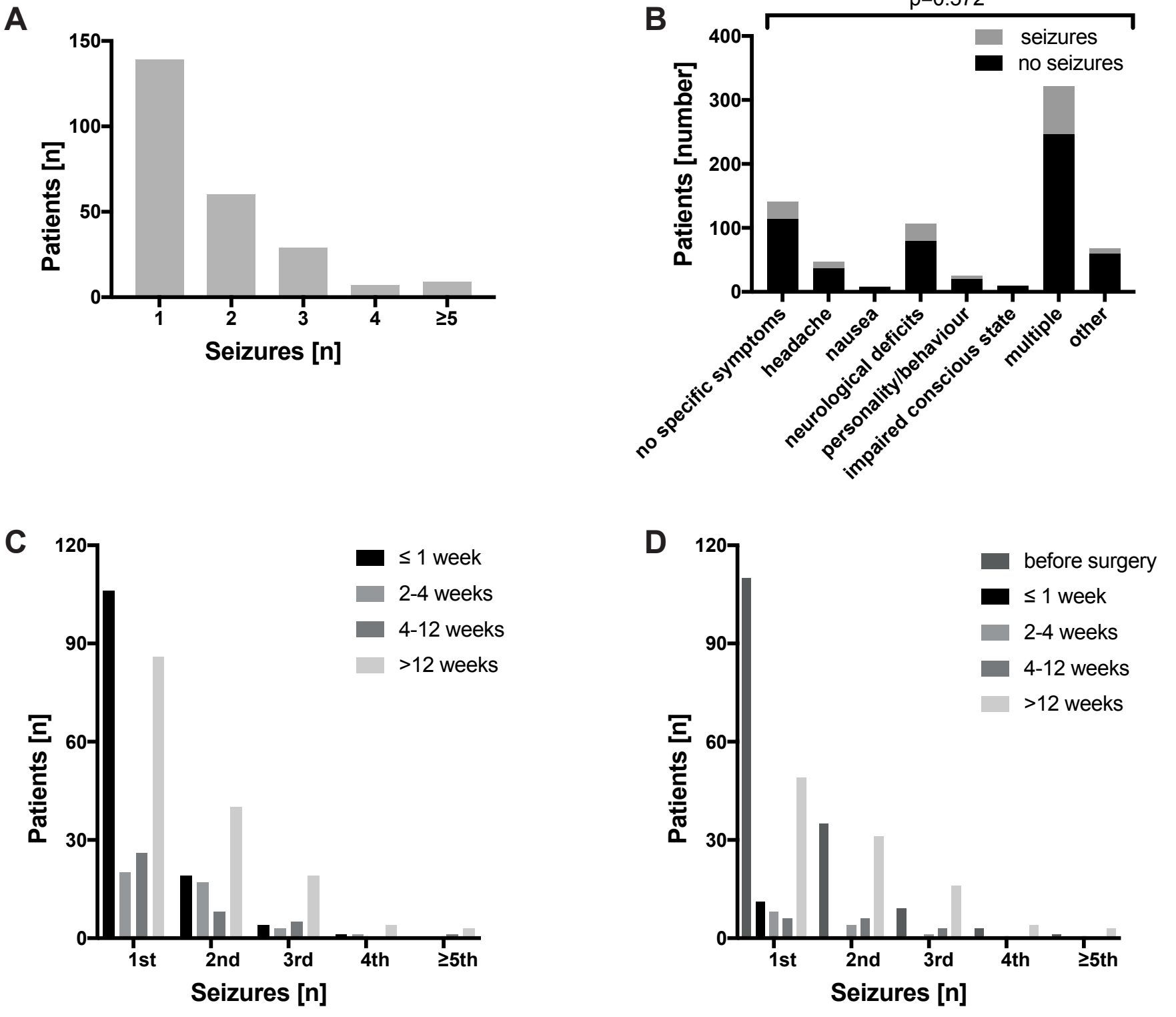

A
150
100
50
0
Patients [n]
1
2
3
4
≥5
Seizures [n]
B
p=0.572
seizures
no seizures
400
300
200
100
0
Patients [number]
no specific symptoms
headache
nausea
neurological deficits
personality/behaviour
impaired conscious state
multiple
other
C
120
90
60
30
0
Patients [n]
≤ 1 week
2-4 weeks
4-12 weeks
>12 weeks
1st
2nd
3rd
4th
≥5th
Seizures [n]
D
120
90
60
30
0
Patients [n]
before surgery
≤ 1 week
2-4 weeks
4-12 weeks
>12 weeks
1st
2nd
3rd
4th
≥5th
Seizures [n]

Figure 3

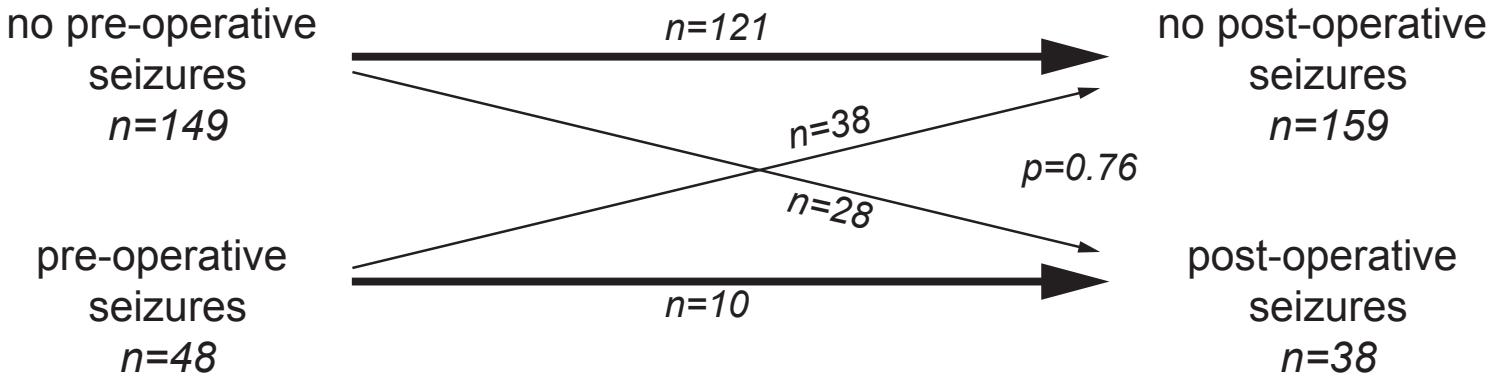
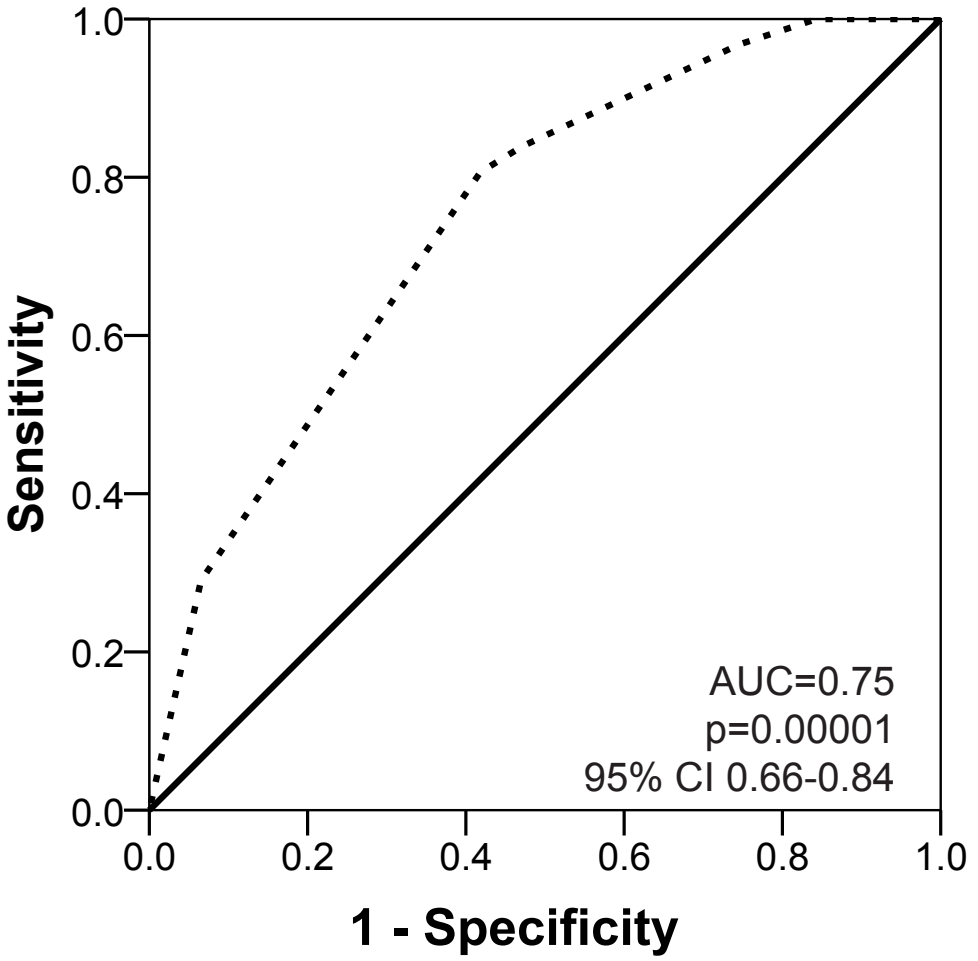

no pre-operative seizures
n=149
pre-operative seizures
n=48
n=121
n=38
n=28
n=10
p=0.76
no post-operative seizures
n=159
post-operative seizures
n=38

Figure 4

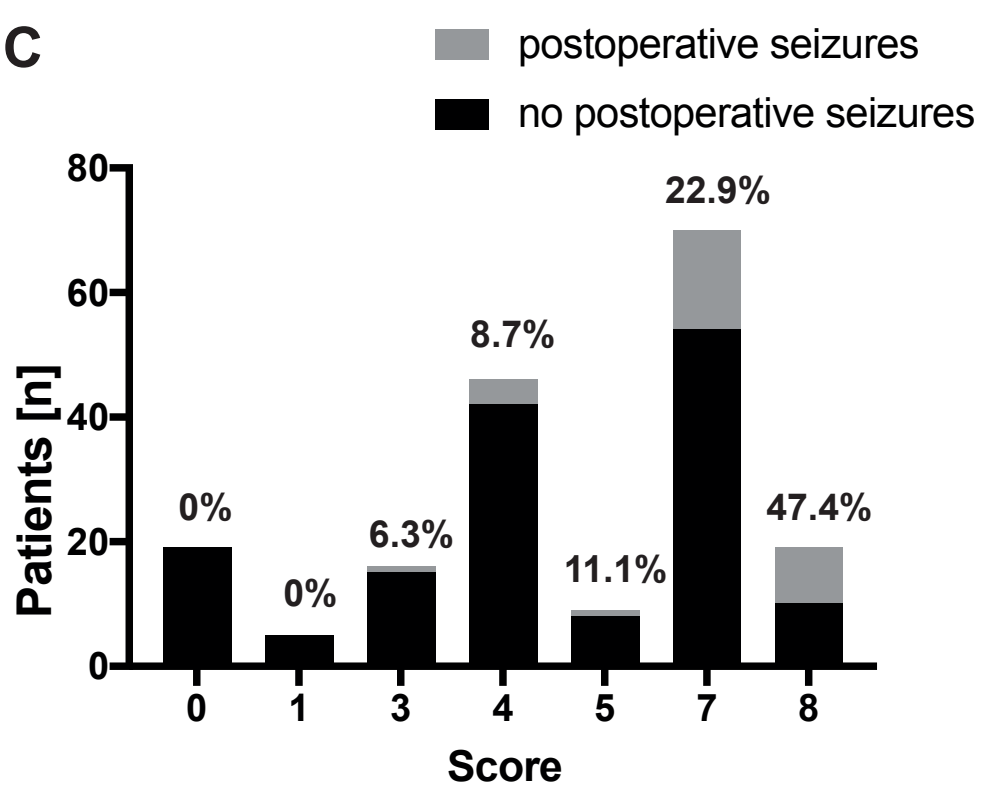
A

	Odds Ratio (95% CI)	P=
Incomplete resection (y/n)	4.6 (1.6-13.1)	0.005
Supratentorial localization (y/n)	5.8 (1.4-24.3)	0.017
Multiple surgeries (y/n)	1.9 (0.9-4.0)	0.095

B



C



Underweight and weight loss are predictors of poor outcome in patients with brain metastasis

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RT no conflict of interest declared

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RT no conflict of interest declared

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Abstract

PURPOSE: Overweight may be associated with favorable outcome whereas tumor cachexia may be associated with worse outcome in patients with metastatic cancer. Here we evaluate the association of abnormal body mass index and weight change with outcome in patients with brain metastasis.

METHODS: Patients with a diagnosis of brain metastasis treated at the University Hospital Zurich (n=703) were assessed for associations of body mass index, weight change, comorbidities and survival.

RESULTS: Compared with patients with normal body mass index of 18.5-24.9 kg/m^2 and a median overall survival of 9 months (95% confidence interval 7.5-10.5), overall survival was inferior in patients with body mass index<18.5 kg/m^2 (overall survival 6 months, 95% confidence interval 1.6-10.3, p=0.04), but superior in patients with body mass index>25 kg/m^2 (overall survival 13 months, 95% confidence interval 11.0-15.0; p=0.033). We report a median relative weight loss of 5% within the first 6 months of diagnosis of brain metastasis (95% confidence interval 3.3-6.5), and reduction exceeding the median was associated with an unfavorable outcome (weight loss <5% 22.0 months, 95% confidence interval 19.2-24.8; weight loss >5% 14.0 months, 95% confidence interval 11.9-16.).

CONCLUSION: High body mass index is associated with better, and underweight with worse outcome in patients with brain metastasis. Conversely, weight loss above median may predict poor outcome. Future studies need to address whether vigorous treatment of tumor cachexia, e.g. by specific nutrition management, might improve outcome of patients with brain metastasis. In contrast, regimens associated with weight loss such as ketogenic diet may be detrimental.

Keywords: cachexia; denutrition; BMI; cerebral; prognosis

1. Introduction

Approximately one fourth of all cancer patients develop brain metastases during their course of disease [1, 2]. Factors associated with favorable outcome in these patients include low number of brain metastases, young age, high Karnofsky performance score (KPS), absence of extracranial metastases and controlled primary tumor [1, 3]. Several reports have described a superior outcome of obese patients in different tumor entities including lung, gastric or colorectal cancer [4-7] at different disease stages, also referred to as the obesity paradox in cancer. Obese patients with distant metastases from various tumors were recently reported to have better survival than normal weight patients [8]. In other cancer types, most importantly breast cancer, however, inferior outcome has been linked to increased BMI [9, 10]. The obesity paradox seems not to hold true for patients with primary brain tumors. One study found no association with survival [11], others report a dismal prognosis for obese patients with glioma [12, 13].

In a retrospective study evaluating 624 lung cancer patients with brain metastases, underweight (BMI<18.5 kg/m^2) was identified as an independent negative prognostic factor [14], however, no contemporary data are available for other tumor entities. Furthermore, it is unclear whether weight loss is associated with outcome. In the present retrospective cohort analysis, we evaluate an association of the BMI at diagnosis of brain metastasis as well as weight loss during the course of disease with outcome in brain metastasis patients and derive potential implications for clinical management.

2. Patients and Methods

Patients were identified by review of the electronic chart system of the University Hospital Zurich (USZ) using the search term “brain metastasis”. Data were obtained by authors AL and BG, quality of data was verified by author FW during regular joint meetings for data review, plausibility checks and random controls. Between 2004 and 2016, 811 patients with the diagnosis of brain metastasis were identified. Information on body weight four weeks around the time of diagnosis of brain metastasis was available for 703 patients, of these, 553 patients (78.7%) were followed up until death. Of the remaining patients, 33 patients (4.7%) were alive at a median follow-up of 31.0 months, and 117 patients (16.6%) were lost to follow-up at a median follow-up of 12 months. Time from diagnosis of the primary tumor was determined by the original histology report. This study was approved by the Cantonal Ethics Committee Zurich (KEK-ZH-Nr. 2018-00192). Consent was obtained according to local regulations. The patient selection path is demonstrated in Figure 1 (CONSORT chart).

BMI was calculated as follows: $BMI=weight/(height)^2$. Furthermore, body weight was assessed 6 months after the diagnosis of brain metastasis, an information that was available for 173 of 703 patients. The primary variables of interest were BMI, vascular comorbidities (including ischemic stroke, subdural hematoma, deep venous thrombosis, myocardial infarction, peripheral arterial occlusive disease, pulmonary embolism, multiple vascular diseases and other extracranial thrombosis), steroid intake at the time of diagnosis and survival. Overweight was graded according to the WHO criteria (underweight: BMI<18.5 kg/m^2; normal weight: BMI 18.5-24.9 kg/m^2; pre-adipositas: BMI 25.0-29.9 kg/m^2; adipositas grade I: BMI 30.0–34.9 kg/m^2; adipositas grade II: BMI 35.0–39.9 kg/m^2; adipositas grade III / adipositas permagna:

BMI≥40.0 kg/m^2). Pre-adipositas and adipositas grades I-III (BMI≥25.0) were grouped together and termed overweight for selected analyses. Information on comorbidities such as diabetes (available for 520 of 703 patients) or arterial hypertension (available for 660 of 703 patients) or vascular risk factors such as smoking were extracted from the medical reports or electronic chart. Pack years (PY) were determined for assessment of smoking as documented in the electronic chart. Individuals with ongoing nicotine consumption and more than 1 PY were rated as smokers. If nicotine consumption was stopped more than 10 years before the diagnosis of brain metastasis, patients were rated as non-smokers. Alcohol consumption was calculated in grams per day according to documented amount of alcoholic beverages in the electronic chart. A regular daily alcohol consume of more than 20 g/d was rated as abuse, according to the guidelines of the Swiss Federeal Alcohol Commission (EKAL) https://www.bag.admin.ch/bag/de/home/das-bag/organisation/ausserparlamentarische-kommissionen/eidgenoessische-kommission-fuer-alkoholfragen-ekal.html. If abuse was reported, but stopped at the time of diagnosis of brain metastasis, it was named as “former abuse”. A HbA1c value > 6.5% (if available) or prior diagnosis documented in the electronic chart were rated as diabetes mellitus. Tumor entities were confirmed by pathology reports from biopsy of the primary tumor or brain metastasis tissue in patients undergoing surgery or both. Graded prognostic assessment scores (GPA) were calculated from age, presence of extracranial metastases, KPS and number of brain metastases, representing the most conserved confounders of survival [3].

Survival times between brain metastasis diagnosis and death were determined from the electronic chart. Median overall survival (OS) was estimated using the Kaplan-

Meier method. Follow-up was documented in the electronic chart, for some patients, additional follow-up information was obtained from the Cancer Registry Zurich and Zug (http://www.en.krebsregister.usz.ch).

Statistical analysis was performed by IBM SPSS statistics ®, Version 23 (IBM Co., Armonk, NY, USA) and GraphPad Prism software, version 7.0 (La Jolla, CA, USA). The Kruskal-Wallis test was used for grouped analysis of unpaired data. We assessed correlations of adipositas grades or weight categories with patient characteristics using Pearson's correlation coefficient. The Log-Rank test was used for assessment of survival differences between groups. Furthermore, a Cox Regression model was applied to identify independent predictors of outcome, with follow-up in months as time scale and items of the GPA score along with dexamethasone intake as possible confounders. Subjects with missing information were not included in multivariate analysis. Significance levels for two-sided p-values were set at $p<0.05$ for significant and $p<0.01$ for highly significant results. The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

3. Results

3.1. Patient database screening and characteristics

Information on BMI from 2 weeks before to 2 weeks after diagnosis of brain metastasis by CT or MR imaging of the brain was available for 703 patients, 108 patients were omitted from further evaluation. Patient characteristics are summarized in Table 1. We assessed correlations of adipositas grades or weight categories with patient characteristics. The items of the GPA score [3] that have been previously shown to be associated with survival of brain metastasis patients were confirmed in

our cohort (age: p=0.005; number of brain metastases p=0.0004; absence/presence of extracranial metastases p=0.011; KPS p=0.001, all Log-Rank test, data not shown). We found no correlation of BMI with age (n=687; r=0.055, p=0.148, Pearson's Correlation, data not shown) or adipositas grades with age (n=684; p=0.213, Kruskal-Wallis test, Figure S1A) or adipositas grades with time from diagnosis of the primary tumor (n=214; p=0.291, Kruskal-Wallis test, data not shown). We also found no association of adipositas grades with steroid intake at the time of diagnosis of brain metastasis (n=552; p=0.475, Chi-Square test, data not shown). Between adipositas grades and KPS, there was evenly no association (n=630; p=0.061, Kruskal-Wallis test, Figure S1B). The median number of brain metastases was insignificantly lower in patients with overweight ($median_{brain\ metastasis}$=1) compared to underweight ($median_{brain\ metastasis}$=2) or normal weight ($median_{brain\ metastasis}$=2) (n=683; p=0.142, Kruskal-Wallis test, Figure S1C). We furthermore found no association between adipositas grades and primary tumors (n=684; p=0.305, Chi-Square test, Figure S1D), fraction of operated patients (n=681; p=0.634, Chi-Square test, Figure S1E) or presence of extracranial metastases (n=525; p=0.727, Chi-Square test, Figure S1F). The fraction of patients pretreated with chemotherapy was similar between WHO adipositas grades (p=0.346, Chi-Square test, data not shown) or weight categories (p=0.753, Chi-Square test, data not shown). We assessed WHO adipositas grades and treatment strategies for patients with the first diagnosis of BM between 2004-2010 versus 2011-2016 as well. There was no difference in terms of distribution of WHO adipositas weight grades (p=0.87, Table S1). However, we observed a significant change in treatment paradigms between the time period from 2004-2010 and 2011-2016: the rate of operated patients was higher for the years from 2004-2010 (94% vs. 63%) whereas

the rate of patients treated with radiotherapy (85% vs. 92%) or chemotherapy (41% vs. 55%) was lower (Table S1). Overall surval did not change between study periods (Table S1).

There was an association between sex and adipositas grades (n=703, p=0.015, Chi-Square test, data not shown) and weight categories (n=703, p=0.014, Chi Square-test, Figure 2A). Post-hoc comparison revealed that the percentage of patients with overweight compared to those with normal weight was higher in the group of males than in females (p=0.003, Chi Square-test, Figure 2A). There was no difference between genders concerning the percentage of patients with underweight compared to those with overweight(p=0.248, Chi-Square test, Figure 2A).

Median weight at the time of diagnosis of brain metastasis was 70.0 kg (95% CI 69.0-71.0) and decreased to 68.0 kg (95% CI 64.0-70.0) after 6 months (Figure S2). Furthermore, we assessed relative weight change by division of weight values from 6 months after the diagnosis of brain metastasis versus time of diagnosis. Median relative weight after 6 months was 0.95, which is equivalent to a median weight loss of 5% (95% CI 3.3 – 6.5%). A relative weight loss of 10% or above was observed in 10 of 173 patients (5.8%).

3.2. Associated comorbidities

Electronic chart review allowed to relate the relevant comorbidities of arterial hypertension, diabetes mellitus and history of neuro- or cardiovascular disease with adipositas and outcome. There was an association between adipositas grades and incidence of arterial hypertension (n=676, p= 0.00001, Chi-Square test). This was confirmed by post-hoc analysis by direct comparison of adipositas grades (all Chi-Square test, see Figure 2B for p-values). Furthermore, there was association

between adipositas grades and diabetes mellitus (n=536; p=0.032, Chi-Square test). Post-hoc analysis by direct comparison, however, confirmed this association only for pre-adipositas patients, but numbers were low for patients with adipositas grades I-III (all Chi-Square test, see Figure 2C for p-values). Since data on smoking were limited for patients with adipositas grades II and III, we pooled all patients with a BMI > 25 kg/m^2 in one weight category termed overweight for further analysis. There was association between smoking (PY) and weight categories (n=585; med_{PY}(underweight)=24.5; med_{PY}(normal weight)=15.0; med_{PY}(overweight)=27.5; p=0.034, Kruskal-Wallis test). Post-hoc analysis by Dunn-Bonferroni-tests confirmed a significant correlation only for the comparison of normal and overweight patients (adjusted p=0.03, Figure 2D). In contrast, we found no association of weight categories with alcohol abuse (n=625; p=0.484, Chi-Square test, data not shown). Median GPA scores of underweight patients were insignificantly lower than in patients with normal or increased weight (n=576; med_{GPA}(underweight)=1.5; med_{GPA}(normal weight)=2; med_{GPA}(overweight)=2; p=0.17, Kruskal-Wallis test, data not shown).

3.3 Survival analyis

Median follow-up was 17.0 months for surviving patients (95% CI 12-23) and median OS was 10.0 months (95% CI 8.7–11.3) for all patients. Bodyweight was associated with outcome across the different adipositas grades (p=0.003, Log-Rank test, Figure S3). There was a significant association between survival and weight categories: patients with normal weight (OS 9 months, 95% CI 7.5 -10.5) showed better OS than underweight patients (OS 6 months, 95% CI 1.6-10.3, p=0.047, Log-Rank test), but an inferior outcome compared to those with overweight (OS 13 months, 95% CI

11.0-15.0, p=0.033 Log-Rank test, Figure 3A). A sub-analysis of lung tumors only showed a better outcome of patients with normal weight (OS 12 months, 95% CI 9.1-14.9) than in those with underweight (OS 5 months, 95% CI 0.1-10.1, p=0.005, Log-Rank test) and similar survival as in those with overweight (OS 15 months, 95% CI 11.9-18.1, p=0.55) (Figure 3B). In patients with brain metastasis from other (non-lung) tumors, there was no survival difference between patients with normal weight (OS 8 months, 95% CI 6.3.-9.7) and those with underweight (OS 10 months, 95% CI 4.5-15.5; p=0.87, Log-Rank test), but an inferior survival compared to those with overweight (OS 11 months, 95% CI 7.9-14.1, p=0.02, Log-Rank test) (Figure 3C). Further subgroup analysis of primary tumors other than lung was limited by small sample sizes, however the favorable prognosis of patients with overweight was confirmed for patients with brain metastasis from melanoma (p=0.042) and other primary tumors (p=0.041), and by trend for cancer of unknown primary site (p=0.070) (Figure S4).

We also evaluated an association of weight loss after 6 months with overall survival. Patients with a weight loss of greater than the median of 5% showed an inferior outcome (weight loss >5%: 14.0 months, 95% CI 11.9-16.1; weight loss <5%: 22.0 months, 95% CI 19.2-24.8; patients with an OS < 6 months were excluded from analysis) (Figure 3D).

We also assessed survival upon stratification for the vascular risk factors that were associated with weight. We found hypertension to be associated with survival (no arterial hypertension OS 12 months, 95% CI 10.1-13.9 versus arterial hypertension OS 9 months, 95% CI 8.1 -12.1, p=0.021, Log-Rank test) (Figure 3E). For diabetes mellitus, there was an according trend (no diabetes OS 12 months, 95% CI 10.3-13.7, diabetes OS 6 months, 95% CI 3.9 -8.1, p=0.0895, Log-Rank test) (Figure 3F).

We tested underweight together with the items of the GPA score, the gold standard for prognostic assessment in brain metastasis patients and thus the most conserved confounders of survival, in a multivariate Cox Regression model. Here, younger age categories compared with older age (HR 0.68, 95% CI 0.53 – 0.88), lower KPS compared with high KPS (HR 0.66, 95% CI 0.51-0.86), low number of brain metastases compared with multiple brain metastases (HR 0.5, 95%CI 0.39 – 0.64) and absence compared with presence of extracranial metastases (HR 0.78, 95% CI 0.65- 0.95) at the time of diagnosis were associated with good outcome, whereas underweight (BMI<18.5 kg/m^2) compared to normal weight or overweight was independently associated with inferior survival (HR 1.4, 95% CI 1.01 – 1.94) (Table 2). Dexamethasone intake at the time of diagnosis of brain metastasis was not associated with outcome (HR 0.78, 95% CI 0.51 – 1.01). In the group of patients with survival above 6 months, a relative weight loss of 5% or more since diagnosis of brain metastasis was an independent predictor of poor outcome (HR 1.7, 95% CI 1.16 – 2.42), but not the items of the GPA score (Table S2).

4. Discussion

The paradigm that obesity is per se associated with enhanced comorbidities and thus inferior survival has been challenged in recent years. Several studies including some studies on cardiovascular and oncological diseases have shown an unexpectedly superior outcome of obese patients. This has been referred to as the "obesity paradox" [4-7]. The underlying mechanism of the obesity paradox has remained unclear. Overweight has been confirmed as a risk factor for cardiovascular comorbidities such as diabetes mellitus or arterial hypertension in the last decades and was thus thought to be associated with inferior survival [15, 16]. In contrast,

recent reports describe a beneficial outcome of obese patients for coronary heart disease [17] or stroke [18]. However, available data is inconsistent since some subsequent investigations failed to confirm these findings, e.g., for stroke [17-19]. The cardiovascular risk profile of patients from our cohort confirmed a significantly higher incidence of cardiovascular risk factors such as arterial hypertension and diabetes mellitus in overweight patients (Figure 2B,C). Arterial hypertension, but not diabetes mellitus, was also associated with an inferior outcome, indicating that comorbidities shape the course of disease even in brain metastasis patients who are commonly considered to experience short survival (Figure 3E,F).

Tumor cachexia is frequent in patients with metastatic cancer, and substantial evidence has shown cachexia to be associated with unfavorable outcome [4-8]. The latter has been shown recently for patients with brain metastasis from lung cancer [14]. While we confirm these findings, we demonstrate that this observation might not hold true for patients from other tumor entities: OS was significantly lower in lung cancer patients with cachexia (Figure 3B), but there was no such difference in patients from other tumor entities (Figure 3C). Conversely, overweight was associated with superior OS in patients with brain metastasis from other cancer than lung cancer (Figure 3C), but not from lung cancer (Figure 3B). Moreover, weight loss after 6 months above the median of 5% was associated with an inferior outcome in our cohort (Figure 3D).

Why obese brain metastasis patients show a superior outcome remains unclear. Fast progressing and thus consuming tumors might be associated with cachexia, but we found no pattern of primary tumors being associated with certain adipositas grades (Figure S1D). Since cachexia might be a result of end stage disease, we assessed for possible bias from preselection of heavily pretreated patients. However,

neither the rate of patients pretreated with chemotherapy nor the time from cancer diagnosis to first detection of brain metastasis differed by weight categories.

The observation that weight loss is associated with inferior outcome in patients with brain metastasis, is at odds with the fact that therapeutic approaches based on specific nutritional regimens, e.g., the ketogenic diet, which might be associated with reduced body weight, are in the focus of interest of cancer patients and physicians, despite insufficient data from controlled trials [20, 21]. Our database did not allow follow-up on dietary measures, which is a limitation of this study. Since such diets may result in significant weight loss, our findings underscore the need to consider such approaches with caution [20]. Conversely, treatment of tumor cachexia by specific nutrition management might help to improve outcome of brain metastasis patients, in particular from lung cancer, and might be a rewarding objective for future clinical studies.

Authorship statement

All authors agreed with the content and gave explicit consent to submit this publication. Consent from the responsible authorities from involved institutions was obtained prior to submission.

All authors made either substantial contributions to the conception or design of the work, the acquisition, analysis, or interpretation of data, drafted the work or revised it critically for important intellectual content. All authors approved the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figures and tables

Figure 1: (CONSORT) chart. The consort chart shows the selection path for patients to be included in this study. The upper part documents the preselection process to identify all brain metastasis patients, the lower part shows further assessments and subgroup analyses.

Figure 2: Association of weight and vascular risk factors. A. The number of patients (x-axis) and respective sex are shown for each weight category as bar plots (black bars: underweight, dark grey bars: normal weight, light grey: overweight patients). Statistical evaluation was done by Chi-Square test, comparison between groups as indicated by brackets. B,C. Adipositas grades are shown for patients with and without arterial hypertension (B) or with and without diabetes mellitus (C) as stacked columns. Grey bars represent patients with, and black bars patients without, a diagnosis of arterial hypertension (B) or diabetes mellitus (C). Statistical evaluation was done by the Chi-square test, groups were compared as marked with brackets, p-values as indicated below. D. Smoking in PY (y-axis) is shown for each weight category (x-axis) as whisker box-plots. Boxes represent the interquartile range and whiskers the 95% CI, medians are shown as a line. Statistical evaluation was done by Kruskal-Wallis test, p values are indicated with brackets.

Figure 3: Weight and survival. A-C. Kaplan-Meier survival curves are shown for different weight categories, with the y-axis marking percentage of survival and the x-axis time in months. A. Survival in all brain metastasis patients is shown for individuals with underweight (dotted line), normal weight (straight line) and overweight (dashed line). Differences between groups were assessed as marked

with brackets using the Log-Rank test, p-values annotated. Similar curves are shown for subgroups with brain metastasis originating from lung cancer (B) or other primaries (C). D. The curve in (D) shows survival of patients with relative weight loss below (dotted line) or above the median of 5% (straight line). E, F. Survival curves are shown for brain metastasis patients with (dotted line) or without (straight line) the diagnosis of arterial hypertension (E) or diabetes mellitus (F). Head lines above each graph indicates the respective group of patients which was investigated.

Table 1: Characteristics of brain metastasis patients. The upper part shows general characteristics including sex, age, BMI, KPS and incidence of primary tumors. The middle and lower part show information on incidence of cardiovascular risk factors.

Table 2: Multivariate analysis including underweight as candidate prognostic factor. The results of multivariate testing of candidate prognostic factors are shown, which were calculated employing a Cox Hazard model. The first column depicts the respective candidate factor, the second one the two-sided p-values, the third column the respective Hazard ratios following 95% CI in the fourth and fifth column.

Supplementary Material

Figure S1: Association of weight and patients characteristics. A-C. Age (A), KPS (B) and number of brain metastases (C) (y-axis) are shown for each WHO adipositas grade (x-axis) (A,B) or per weight category (C) as whisker box-plots. Boxes represent the interquartile range and Whiskers 95% CI, medians are shown as broad, bold lines. Statistical evaluation was done by Kruskal-Wallis test, p values

are indicated with brackets. In C, post-hoc testing by Dunn-Bonferroni-tests is shown with p-values for subgroups as indicated by brackets. D-F. Adipositas grades are shown for each tumor entity (D), operated vs. non-operated individuals (E) and absence versus presence of extracranial metastases as stacked columns (F).

Figure S2: Evolution of weight change. Weight in kg (y-axis) is shown for assessment at the time of diagnosis of brain metastasis and 6 months later (x-axis) as Whisker box-plots. Boxes represent the interquartile range and Whiskers 95% CI, medians are shown as broad, bold lines. Statistical evaluation was done by Wilcoxon test for paired samples, p values are indicated with brackets.

Figure S3: Adipositas grades and survival. A. The Kaplan-Meier curve shows survial for different WHO adipositas grades (see legend for color code), with the y-axis marking percentage of survival and the x-axis time in months. B. OS including 95% CI is annotated for all adipositas grades.

Figure S4: Other tumor types and survival. A-E. The Kaplan-Meier curve shows survial for different subgroups of primary tumors other than lung cancer, including cancer of unknown primary site (A), gastrointestinal cancer (B), breast cancer (C), melanoma (D) and other primary tumors (E). Legends indicate different weight categories according to color code, with the y-axis marking percentage of survival and the x-axis time in months. F. OS including 95% CI is annotated for all primary tumors other than lung-cancer as a table (CUP = cancer of unknown primary site).

Table S1: Characteristics of brain metastasis patients during different periods of the study. The first column shows the respective item which was assessed, the second column results for all patients, the third column results for the first half of the study period, the fourth column for the second half of the stud period and the last column results of statistical testing (all Chi-square test).

Table S2: Multivariate analysis including weight loss after 6 months as candidate prognostic factor. The results of multivariate testing of candidate prognostic factors 6 months after diagnosis of BM are shown, which were calculated employing a Cox Hazard model. The first column depicts the respective candidate factor, the second one the two-sided p-values, the third column the respective Hazard ratios following 95% CI in the fourth and fifth column.

Figure 1 (CONSORT)

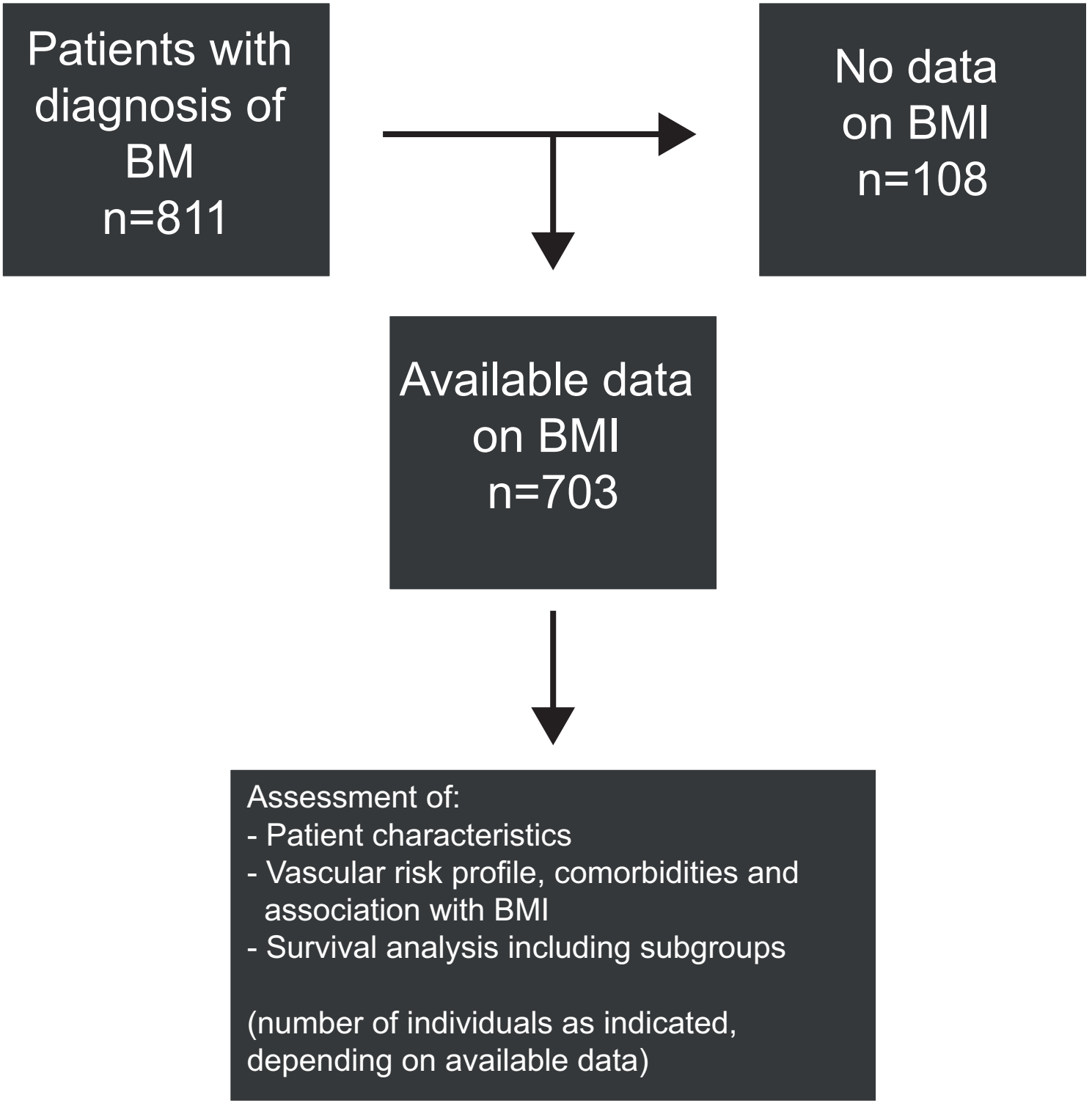
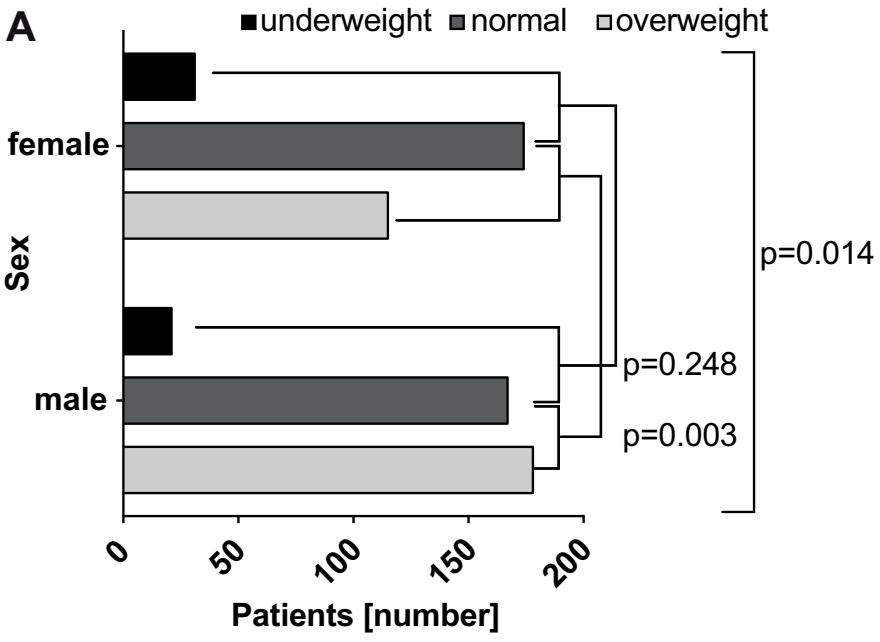
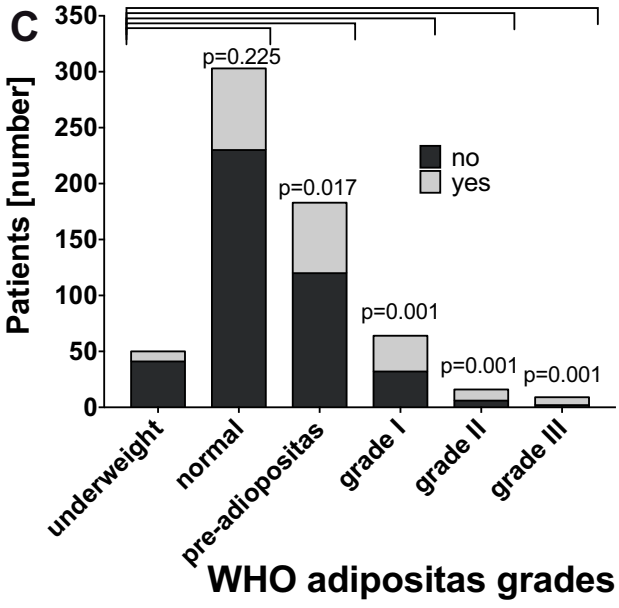
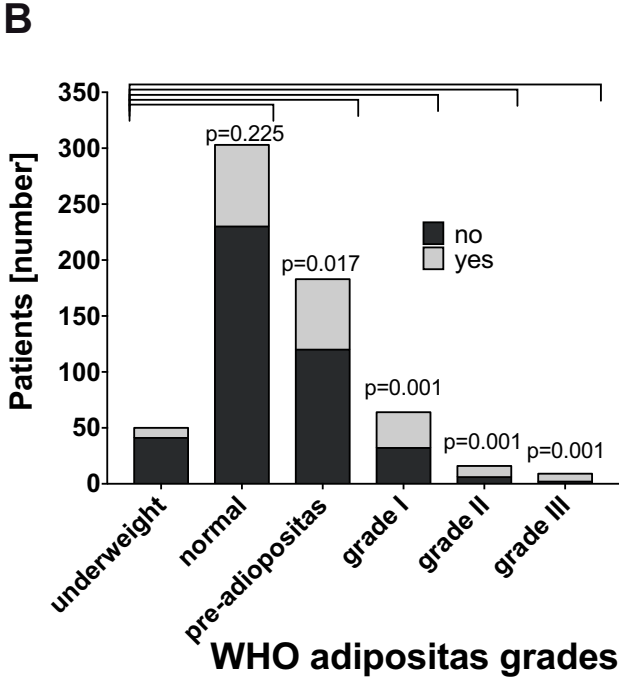


Figure 2


A
underweight
normal
overweight
female
male
Sex
p=0.014
p=0.248
p=0.003
0
50
100
150
200
Patients [number]


C
Patients [number]
350
300
250
200
150
100
50
0
p=0.225
p=0.017
p=0.001
p=0.001
p=0.001
no
yes
underweight
normal
pre-adiopositas
grade I
grade II
grade III
WHO adipositas grades


B
Patients [number]
350
300
250
200
150
100
50
0
p=0.225
p=0.017
p=0.001
p=0.001
p=0.001
no
yes
underweight
normal
pre-adiopositas
grade I
grade II
grade III
WHO adipositas grades

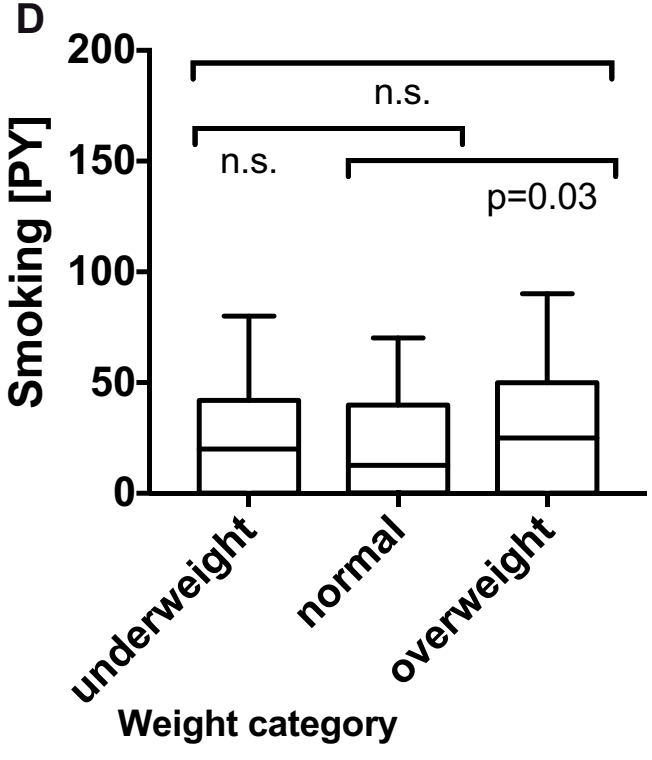

D
Smoking [PY]
200
150
100
50
0
n.s.
n.s.
p=0.03
underweight
normal
overweight
Weight category

Figure 3

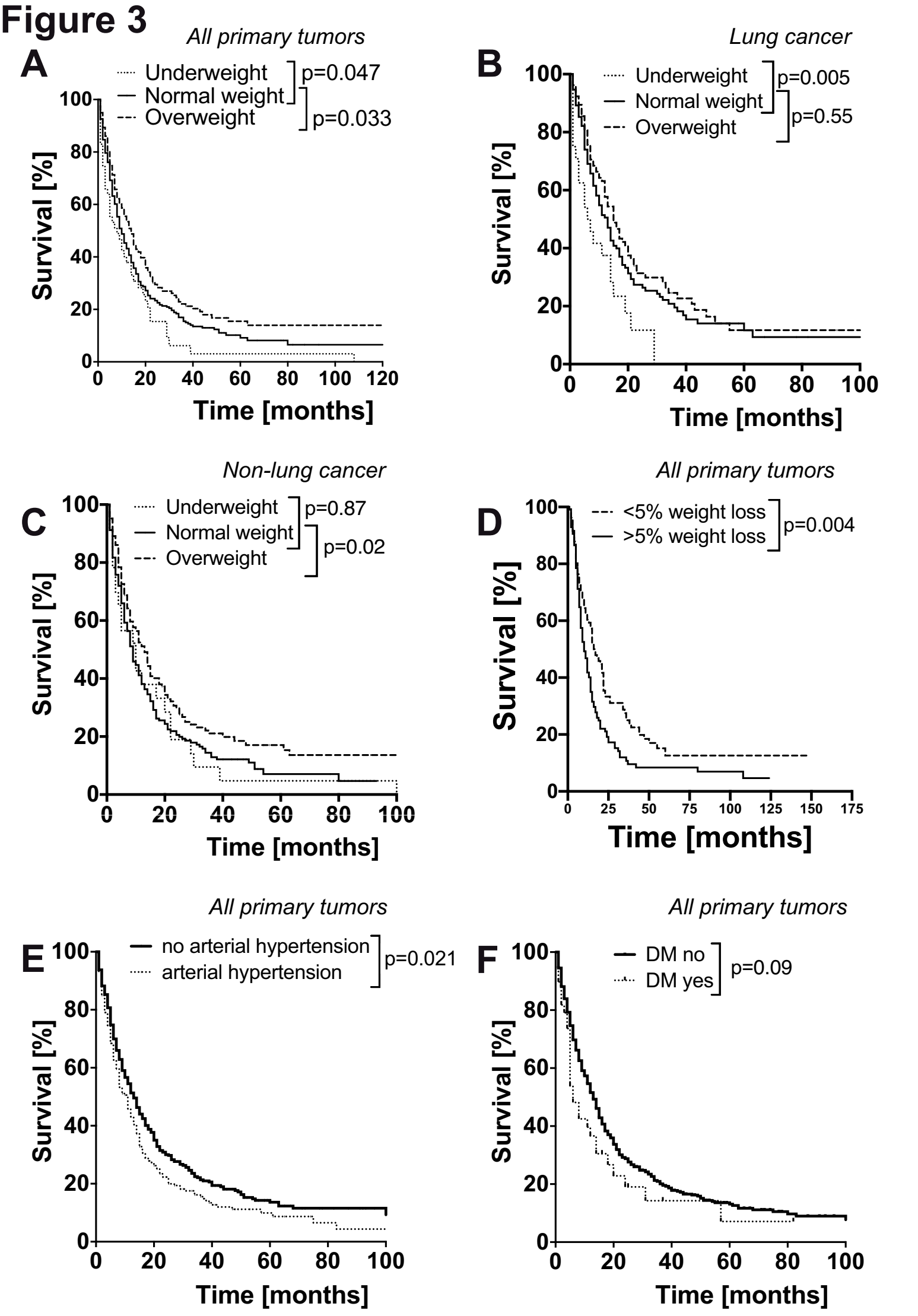

A
All primary tumors
Underweight
Normal weight
Overweight
p=0.047
p=0.033
Survival [%]
Time [months]
B
Lung cancer
Underweight
Normal weight
Overweight
p=0.005
p=0.55
Survival [%]
Time [months]
C
Non-lung cancer
Underweight
Normal weight
Overweight
p=0.87
p=0.02
Survival [%]
Time [months]
D
All primary tumors
<5% weight loss
>5% weight loss
p=0.004
Survival [%]
Time [months]
E
All primary tumors
no arterial hypertension
arterial hypertension
p=0.021
Survival [%]
Time [months]
F
All primary tumors
DM no
DM yes
p=0.09
Survival [%]
Time [months]

Figure S1

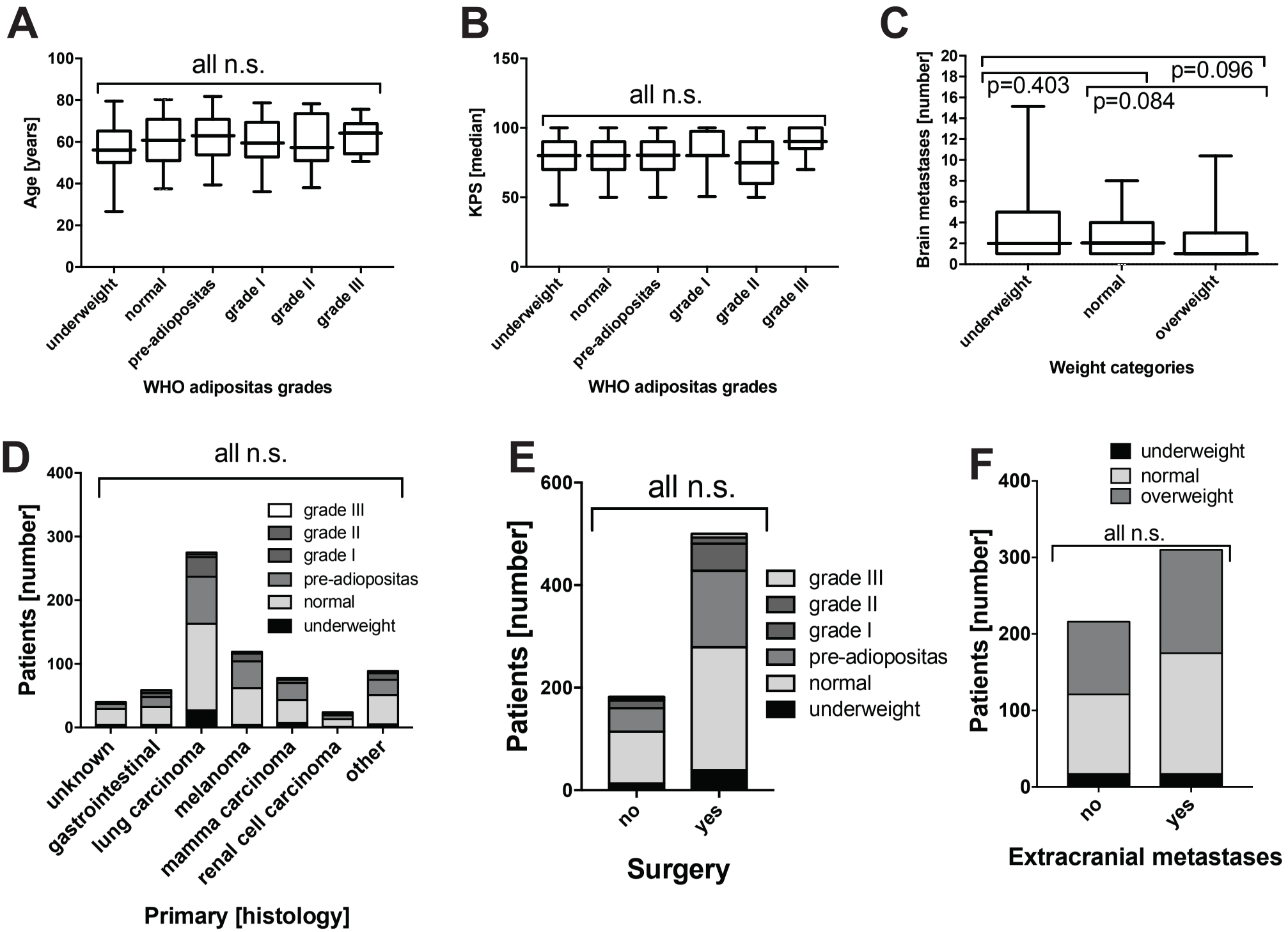

A
all n.s.
Age [years]
100
80
60
40
20
0
underweight
normal
pre-adiopositas
grade I
grade II
grade III
WHO adipositas grades
B
all n.s.
KPS [median]
150
100
50
0
underweight
normal
pre-adiopositas
grade I
grade II
grade III
WHO adipositas grades
C
p=0.403
p=0.096
p=0.084
Brain metastases [number]
20
18
16
14
12
10
8
6
4
2
0
underweight
normal
overweight
Weight categories
D
all n.s.
Patients [number]
400
300
200
100
0
grade III
grade II
grade I
pre-adiopositas
normal
underweight
unknown
gastrointestinal
lung carcinoma
melanoma
mamma carcinoma
renal cell carcinoma
other
Primary [histology]
E
all n.s.
Patients [number]
600
400
200
0
grade III
grade II
grade I
pre-adiopositas
normal
underweight
no
yes
Surgery
F
underweight
normal
overweight
all n.s.
Patients [number]
400
300
200
100
0
no
yes
Extracranial metastases

Figure S2

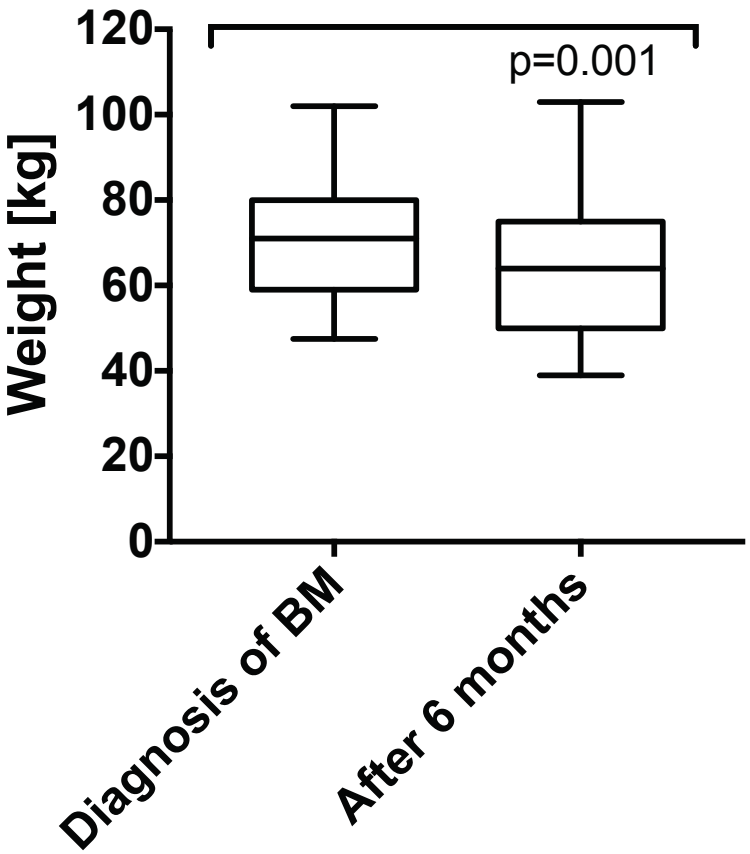
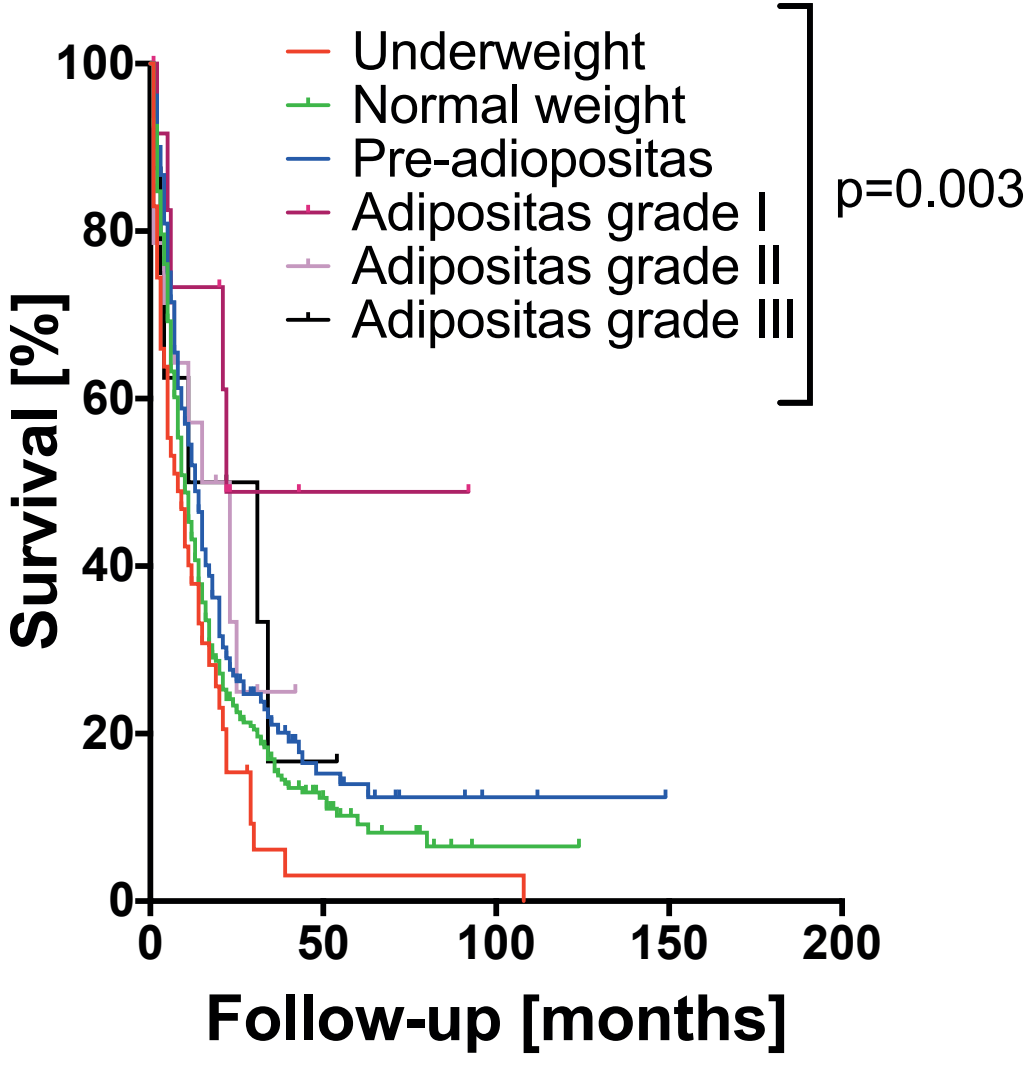

120
100
80
60
40
20
0
Weight [kg]
p=0.001
Diagnosis of BM
After 6 months

Figure S3

A

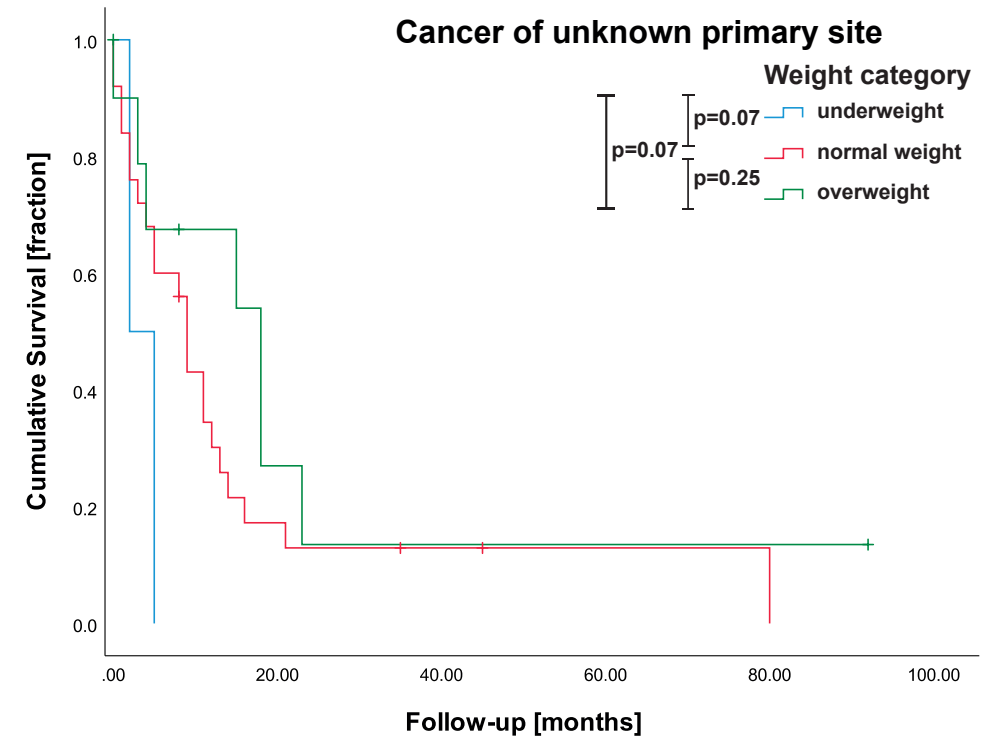


B

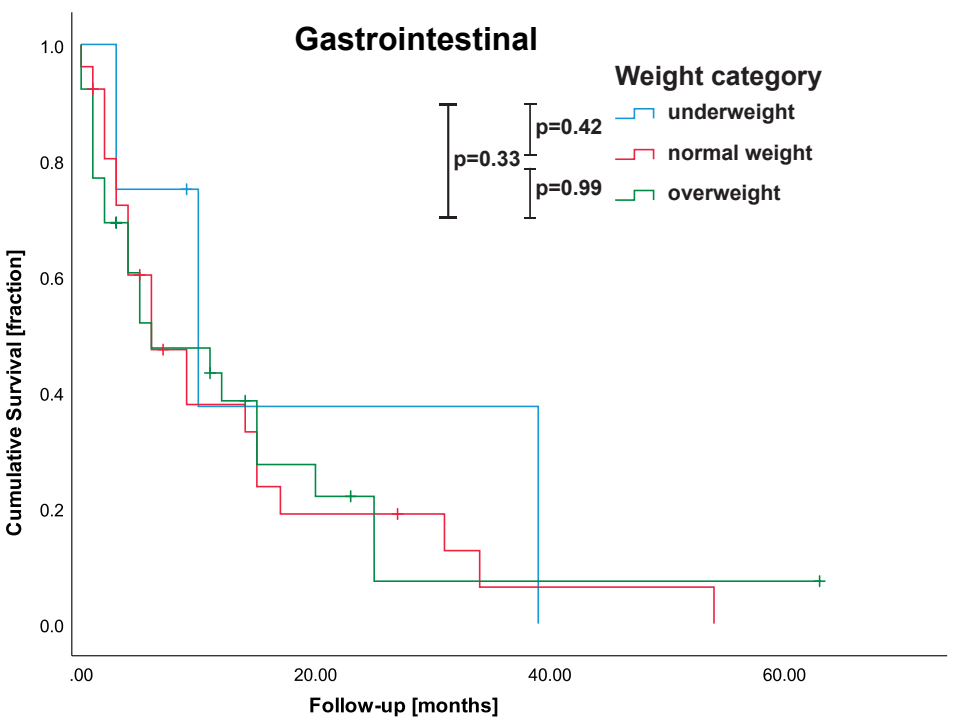
WHO adipositas grades	OS, months (95%CI)
underweight (BMI<18.5)	6 (1.6-10.4)
normal (BMI 18.5-24.9)	9 (7.5.-10.5)
pre-adiopositas (BMI 25.0-29.9)	12 (8.8-15.1)
adipositas grade I (BMI 30.0-34.9)	14 (9.2-18.8)
adipositas grade II (BMI 35.0-39-9)	11 (0.1-25.8)
adipositas grade III (BMI>40)	11 (0.1-31.5)
Overall	11 (9.5-12-5)

Figure S4

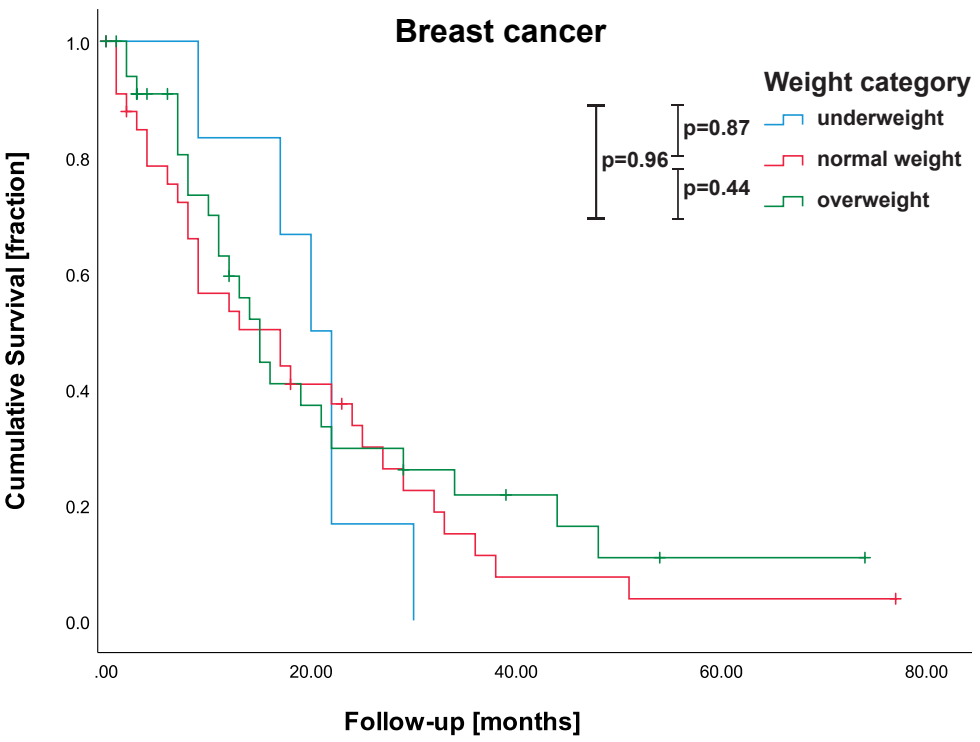
A



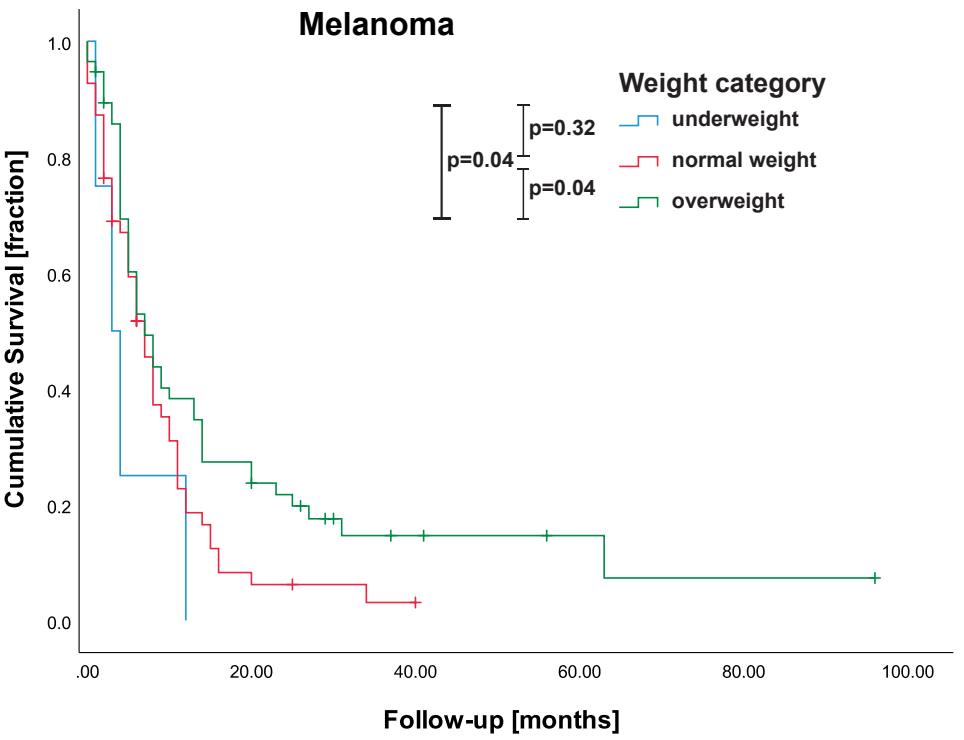
B



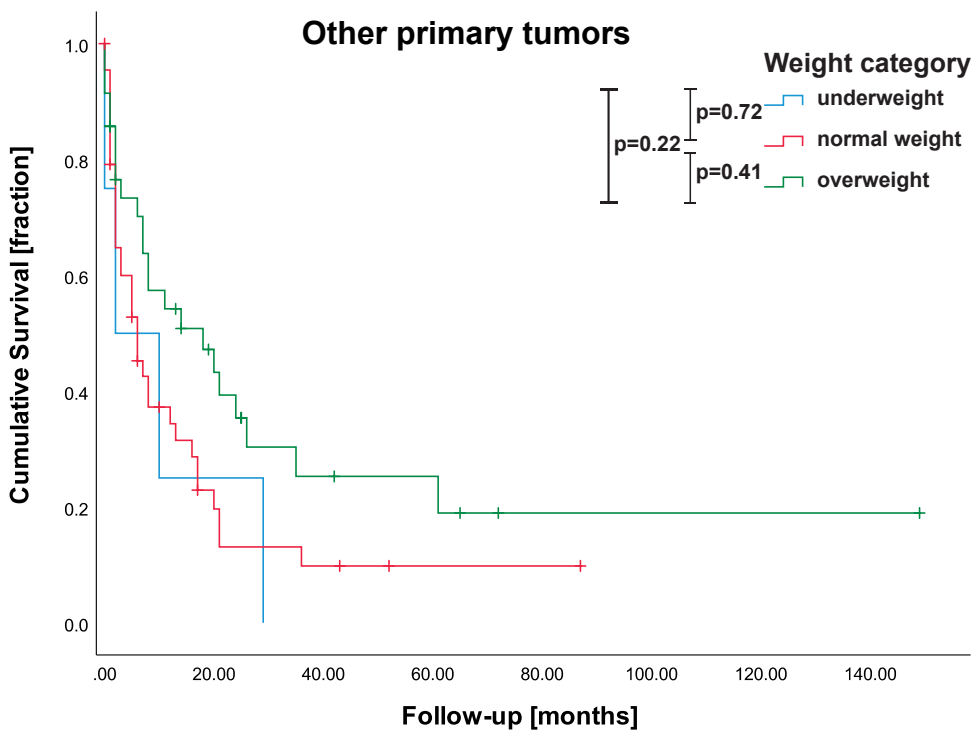
C



D



E



F

		OS (months)	95% CI
CUP			
	underweight	2	0.1 - 4.3
	normal	9	7.5 - 10.5
	overweight	18	7.1 - 28.9
	overall	9	3.4 - 14.6
Gastrointestinal cancer			
	underweight	10	0.0 - 20.5
	normal	6	1.6 - 10.4
	overweight	6	0.0 - 14.0
	overall	6	1.3 - 10.7
Breast cancer			
	underweight	20	16.0 - 24.0
	normal	17	6.0 - 28.0
	overweight	15	11.7 - 18.3
	overall	16	11.6 - 20.4
Melanoma			
	underweight	3	0.1 - 5.9
	normal	7	5.2 - 8.8
	overweight	7	4.6 - 9.4
	overall	7	5.5 - 8.5
Other primary tumors			
	underweight	2	0.0 - 11.8
	normal	6	2.5 - 9.5
	overweight	18	3.1 - 32.9
	overall	8	3.9 - 12.1

Table 1

Sex, number	
male	373
female	330
Sex ratio (male/female)	1.13
Age, median (range)	60.3 (19.3-88.3)
Number of BM, median (range)	2 (1-64)
BMI, median (range)	23.8 (15-51)
Karnofsky Performance Score, median (range)	80 (20-100)
Location of BM, number (%)	
deep brain	8 (1.1)
cerebellum	68 (9.7
brain stem	6 (0.9)
frontal	115 (16.4)
parietal	49 (7.0)
occipital	32 (4.6)
temporal	37 (5.3)
other	10 (0.3)
multiple BM	378 (53.8)
Primary tumor, number (%)	
unknown	40 (5.7)
lung cancer	288 (41.0)
melanoma	126 (17.9)
breast cancer	81 (11.5)
renal cell carcinoma	23 (3.3)
gastrointestinal	58 (8.3)
other	87 (12.4)
Alcohol, number (%)	
no abuse	480 (85.5)
ongoing abuse	74 (10.5)
former abuse	19 (2.9)
no information	58
Prior vascular event, number (%)	
none	589 (83.8)
ischemic stroke	11 (1.6)
subdural hematoma	1 (0.1)
intracranial hemorrhage	1 (0.1)
deep venous thrombosis	23 (3.3)
myocardial infarction	15 (2.1)
peripheral arterial occlusive disease	23 (3.3)
pulmonary embolism	11 (1.6)
multiple	24 (3.4)
other	5 (0.7)
Arterial hypertension, number (%)	
no	473 (68.0)
yes	223 (31.7)
incomplete file	7
Diabetes, number (%)	
no	482 (92.9)
yes	37 (7.1)
no data	184
Smoking, number (%)	
no	218 (36.5)

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yes	380 (63.5)
no data	105
Smoking, pack years; median (range)	20 (0-150)
Steroid intake at diagnosis of BM, number (%)	
no	61 (91.5)
yes	579 (9.5)
no data	63

Table 2: Multivariate cox regression analysis of candidate risk factors associated with survival*

Candidate factors	p=	Hazard Ratio	95% CI	
			Lower	Upper
Age (GPA score: >60y = 0, 50-59y=0.5 ; <50y=1)	0.0057	0.67	0.50	0.89
Number of BM (GPA score: >3=0, 2-3=0.5, 1=1)	0.0003	0.49	0.37	0.64
KPS (GPA score: <70% = 0, 70-80%=0.5 ; 90-100%=1)	0.0083	0.68	0.51	0.91
Extracranial metastases (GPA score: yes=1; none=0)	0.0448	0.80	0.65	0.99
Underweight (BMI<18.5 kg/m^2)	0.0327	1.40	1.03	2.23

* The results of multivariate testing of candidate risk factors for association with survival are shown, which were calculated employing a Cox Hazard model. The first column depicts the respective candidate factor, the second one the two-sided p-values, the third column the respective Hazard Ratios following 95% CI in the fourth and fifth column.

Table S1

	All (n=703)	2004-2010 (n=186)	2011-2016 (n=517)	p=
Adipositas grade n (%)				0.871
underweight (BMI<18.5)	53 (7.5)	14 (7.0)	39 (7.8)	
normal (BMI 18.5-24.9)	380 (54.1)	101 (55.2)	279 (53.8)	
pre-adiopositas (BMI 25.0-29.9)	183 (26.0)	49 (26.4)	134 (25.6)	
adipositas grade I (BMI 30.0-34.9)	64 (9.1)	16 (8.0)	48 (9.6)	
adipositas grade II (BMI 35.0-39-9)	13 (1.8)	2 (2.0)	11 (1.8)	
adipositas grade III (BMI>40)	10 (1.4)	4 (1.5)	6 (1.4)	
Surgery n (%)				
No	203 (28.9)	11 (5.9)	192 (37.1)	<0.001
Yes	500 (71.1)	175 (94.1)	325 (62.9)	
Radiotherapy n (%)				
No	69 (10.2)	26 (15.0)	43 (8.5)	0.015
Yes	608 (89.8)	147 (85.0)	461 (91.5)	
Incomplete file	26			
Chemotherapy after diagnosis of BM n (%)				
no	344 (49.1)	109 (59.2)	235 (45.5)	0.001
yes	356 (50.9)	75 (40.8)	281 (54.5)	
Incomplete file	3			
Overall survival, months (95% CI)	10 (8.7-11.3)	10.0 (7.3-12.7)	10.0 (8.7-11.5)	

Table S2: Multivariate cox regression analysis of candidate risk factors associated with survival after 6 months*

Candidate factors	p=	Hazard Ratio	95% CI	
			Lower	Upper
Age (GPA score: >60y = 0, 50-59y=0.5 ; <50y=1)	0.167	0.713	0.44	1.15
Number of BM (GPA score: >3=0, 2-3=0.5, 1=1)	0.316	0.768	0.46	1.29
KPS (GPA score: <70% = 0, 70-80%=0.5 ; 90-100%=1)	0.629	0.880	0.53	1.48
Extracranial metastases (GPA score: yes=1; none=0)	0.522	0.888	0.62	1.28
Weight loss (more than 5% within the first 6 months)	0.006	1.676	1.16	2.42

* The results of multivariate testing of candidate risk factors for association with survival are shown, which were calculated employing a Cox Hazard model. The first column depicts the respective candidate factor, the second one the two-sided p-values, the third column the respective Hazard Ratios following 95% CI in the fourth and fifth column.

Table 1. Patient characteristics stratified for absence versus presence of BTRE⁺.

	All patients (n=799)	No BTRE (n=573, 71.7%)	Confirmed BTRE (n=226, 28.3%)	p*=
Sex, m/f	427/372	*298/275*	*129/97*	0.284[a]
Age, median (range)	60.5 (20.5-90.1)	*60.9 (20.5-90.1)*	*58.4 (26.6-84.9)*	**0.004***[b]
Number of BM, median (range)	2 (1-64)	*2 (1-64)*	*1 (1-20)*	0.095[b]
KPS, median (range)	80 (20-100)	*80 (30-100)*	*80 (20-100)*	0.829[b]
Primary tumor, n (%)				
unknown	45 (5.6)	*34 (75.6)*	*11 (24.4)*	0.556[a]
lung cancer	332 (41.6)	*225 (67.8)*	*107 (32.2)*	**0.037**[a]
melanoma	143 (17.9)	*105 (73.4)*	*38 (26.6)*	0.616[a]
breast cancer	93 (11.6)	*76 (81.7)*	*17 (18.3)*	**0.023**[a]
renal cell cancer	28 (3.5)	*20 (71.4)*	*8 (28.6)*	0.973[a]
gastrointestinal cancer	63 (7.9)	*46 (73.0)*	*17 (270)*	0.811[a]
other	95 (11.9)	*66 (68.8)*	*30 (31.3)*	0.784[a]
Alcohol, n (%)				
no abuse	624 (85.5)	*444 (71.5)*	*180 (28.5)*	Ref.
ongoing abuse (> 30g/d)	84 (11.5)	*54 (64.3)*	*30 (35.7)*	0.420[a]
former abuse	22 (3.0)	*16 (72.7)*	*6 (27.3)*	0.812[a]
no information	81			
First seizure, type, n (%)				
focal seizures (intact awareness)	83 (36.7)			
focal seizures (impaired awareness)	21 (9.3)			
generalized tonic-clonic (onset unknown)	92 (40.7)			
generalized, non-motor (onset unknown)	8 (3.5)			
status epilepticus	12 (5.3)			
incomplete file	10			
AED prophylaxis, n (%)				
no primary prophylaxis	573 (72.7)	*395 (68.9)*	*178 (31.1)*	Ref.
primary prophylaxis	150 (19.0)	*104 (69.3)*	*46 (30.7)*	0.582[a]
perioperative prophylaxis	65 (8.2)			
Localization of BM, n (%)				
deep brain	8 (2.6)	*8 (100.0)*	*0 (0.0)*	0.942[a]
cerebellum	64 (21.1)	*57 (89.1)*	*7 (10.9)*	0.899[a]
brain stem	6 (2.0)	*5 (83.3)*	*1 (16.7)*	0.798[a]
frontal	110 (36.2)	*62 (56.4)*	*48 (43.6)*	0.094[a]
parietal	49 (16.1)	*32 (65.3)*	*17 (34.7)*	0.809[a]
occipital	27 (8.9)	*16 (59.3)*	*11 (40.7)*	0.886[a]
temporal	39 (12.8)	*32 (82.1)*	*7 (17.9)*	0.121[a]
supratentorial	226 (74.3)	*142 (62.8)*	*84 (37.2)*	**<0.001**
infratentorial	78 (25.7)	*70 (89.7)*	*8 (10.3)*	Ref.
missing information	61			
multiple BM	434			
Surgery, n (%)				
no surgery	242 (30.3)	*193 (79.8)*	*49 (20.2)*	Ref.
one or more surgeries	557 (69.7)	*380 (68.2)*	*177 (31.8)*	**0.001**[a]
file incomplete	2			
Extent of resection of supratentorial single BM				
no surgery	28 (17.0)			
biopsy	1 (0.6)			
partial resection	87 (52.7)			
gross total resection	49 (29.3)			
no post-operative MRI	61			
Treatments administered after BM diagnosis in non-operated patients, n (%)				
no chemotherapy or RT	9 (3.8)			
RT only	103 (43.1)			

chemotherapy only	5 (2.1)			
chemotherapy and radiotherapy	122 (51.0)			
incomplete file	4			
no radiotherapy	14 (5.9)	*12 (85.7)*	*2 (20.7)*	Ref.
radiotherapy	224 (94.1)	*177 (79.0)*	*47 (21.0)*	0.553[a]
no chemotherapy	114 (47.1)	*91 (79.8)*	*23 (20.2)*	Ref.
chemotherapy	128 (52.9)	*101 (78.9)*	*27 (21.1)*	0.860[a]
Treatments administered after surgery of BM, n (%)				
no chemotherapy or RT	*58 (11.0)*			
RT only	*216 (41.1)*			
chemotherapy only	*12 (2.3)*			
chemotherapy and radiotherapy	*239 (45.5)*			
incomplete file	*32*			
no radiotherapy	72 (13.6)	*58 (80.6)*	*14 (19.4)*	Ref.
radiotherapy	456 (86.4)	*300 (65.8)*	*156 (34.2)*	**0.013**
no chemotherapy	296 (53.5)	*218 (73.6)*	*78 (26.4)*	Ref.
chemotherapy	257 (46.5)	*158 (61.5)*	*99 (38.5)*	**0.002**

+ The results of database screening are shown. The first column depicts the respective characteristics item, with main items in bold letters and sub-characters in normal letters. The second column shows overall values for all patients, values as indicated. Percentages for sub-items reflect their fraction compared to the whole entity of a main item. The third and fourth columns show the fraction of patients without and with seizures, marked with italic letters. Percentages refer to the fraction of patients with or without seizures for each item. RT indicates radiotherapy of the brain.

*Results of statistical testing, indicating p-values. Significant values are highlighted with bold letters, the respective statistical test is indicated with superscript letters: a = Chi square test; b = Mann-Whitney U test; Ref. = group of patients that served as a reference.

Table 2. Characteristics of operated BM patients and risk factors for post-operative seizures[+].

	All operated patients (n=557)	**No post-operative seizures (n=471, 84.6%)**	**One or more post-operative seizures (n=86, 15.4%)**	**P=**
Sex, m/f	291/266	*247/224*	*44/42*	0.827[a]
Age, median (range)	61.9 (22.9-90.1)	*62.2 (22.9-90.1)*	*60.6 (31.7-84.9)*	0.073[b]
Number of BMs, median (range)	1 (1-36)	*1 (1-36)*	*1 (1-20)*	0.854[b]
KPS, % (range)	80 (20-100)	*80 (30-100)*	*80 (20-100)*	0.988
Primary tumor, n (%)				0.479[a]
unknown	39 (7.4)	*35 (89.7)*	*4 (10.3)*	0.342 [a]
lung cancer	224 (40.2)	*183 (81.7)*	*41 (18.3)*	0.085 [a]
melanoma	90 (16.2)	*76 (84.4)*	*14 (15.6)*	0.956 [a]
breast cancer	64 (11.5)	*56 (87.5)*	*8 (12.5)*	0.307 [a]
renal cell cancer	23 (4.1)	*22 (95.7)*	*1 (4.3)*	0.130 [a]
gastrointestinal cancer	53 (7.0)	*47 (88.7)*	*6 (11.3)*	0.540 [a]
other	64 (11.5)	*52 (81.3)*	*12 (18.8)*	0.585 [a]
Number of BM, n (%)				
single BM	239 (43.2)	*203 (84.9)*	*36 (15.1)*	Ref.
multiple BM	314 (56.8)	*265 (84.4)*	*49 (15.6)*	0.861 [a]
incomplete file	1			
Localization of BM (supratentorial *versus* infratentorial), n (%)				
single supratentorial BM	198 (75.9)	*160 (80.8))*	*38 (19.2)*	**0.012**
single infratentorial BM	66 (25.0)	*62 (93.9)*	*4 (6.1)*	Ref.
Localization of single supratentorial BM, n (%)				**0.020[a]**
frontal	94 (47.5)	*80 (85.1)*	*14 (14.9)*	0.144[a]
parietal	44 (22.2)	*34 (77.3)*	*10 (22.7)*	0.500[a]
occipital	25 (12.6)	*16 (64.0)*	*9(36.0)*	**0.027[a]**
temporal	33 (17.2)	*30 (88.2)*	*4 (11.8)*	0.022[a]
Depth of single supratentorial BM, n (%)				
cortical or sub-cortical	175 (88.8)	*144 (82.3)*	*31 (17.7)*	0.114[a]
other	22 (11.2)	*15 (68.2)*	*7 (31.8)*	Ref.
Number of surgeries, n (%)				**0.039 [b]**
one brain surgery	456 (81.9)	*401 (87.9)*	*55 (12.1)*	Ref.
two or more brain surgeries	101 (18.1)	*70 (69.3)*	*31 (30.7)*	**<0.001[b]**
Cerebral venous thrombosis, n (%)				
no	547 (98.3)	*465 (84.7))*	*82 (15.3)*	Ref.
yes	10 (1.7)	*6 (60.0)*	*4 (40.0)*	**0.030**
Extent of resection of supratentorial single BM, n (%)				**0.011**
Biopsy	2 (1.4)	*1 (100.0)*	*0 (0)*	Ref.
partial resection	87 (63.0)	*63 (72.4)*	*24 (27.6)*	
gross total resection	49 (35.5)	*45 (91.8)*	*4 (8.2)*	**0.008**

[+] The first column depicts the respective characteristics item, with main items in bold letters and sub-items in normal letters. The second column shows overall values for all patients, values as

indicated. Percentages for sub-items reflect their fraction. The third and fourth column show the fraction of patients without and with seizures. Percentages refer to the fraction of patients with or without seizures for each item.

* Results of statistical testing, indicating p-values. Significant values are highlighted with bold letters, the respective statistical test is indicated with superscript letters: a, Chi square test; b, Mann-Whitney U test, Ref. = group of patients that served as the reference.

Table S1. AED and their sequence in combination therapy[+].

AED agent	1st	2nd	3rd	4th	5th
Valproic acid	22	9	3	0	1
Levetiracetam	85	16	2	1	0
Phenytoin	52	5	1	0	0
Carbamazepine	5	7	0	0	0
Phenobarbital	2	4	1	0	0
Lamotrigine	2	4	2	0	0
Benzodiazepins	23	39	8	0	0
other	6	0	0	0	0
on AED	197	84	17	1	1
no AED	29	142	209	225	225

[+] AED used for secondary seizure prophylaxis in BM patients with BTRE are shown. The first column shows the respective AED, the subsequent columns depict the number of patients which received the respective agent as a first to fifth line of seizure prophylaxis. The second lowest line shows all patients with, and the lowest line all patients without, the respective line of AED treatment.

Table S2. Characteristics of non-operated BM patients.[+]

	All patients (n=242)	**No BTRE (n=193, 79.8%)**	**Confirmed BTRE (n=49, 20.2%)**	***p=**
Sex, m/f	134/107	*103/88*	*30/19*	0.359[a]
Age, median (range)	56.8 (20.5-85.2)	*57.0 (20.5-85.2)*	*55.2 (26.6-79.8)*	0.182[b]
KPS, median (range)	85 (20-100)	*80 (40-100)*	*90 (20-100)*	0.857[b]
Number of BM, median (range)	4 (1-64)	*4 (1-64)*	*2 (1-19)*	**0.013[b]**
one single BM (n, %)	51 (21.3)	*34 (66.7)*	*17 (33.3)*	**0.007[a]**
multiple BM (n, %)	189 (78.7)	*158 (83.6)*	*31 (16.5)*	Ref.
incomplete file	2			
Primary tumor, n (%)				0.816[a]
unknown	6 (2.5)	*5 (83.3)*	*1 (16.7)*	
lung cancer	108 (44.6)	*89 (82.4)*	*19 (17.6)*	
melanoma	53 (21.9)	*41 (77.4)*	*12 (22.6)*	
breast cancer	29 (12.0)	*23 (79.3)*	*6 (20.7)*	
renal cell cancer	5 (2.1)	*3 (60.0)*	*2 (40.0)*	
gastrointestinal	10 (4.1)	*9 (90.0)*	*1 (10.0)*	
other	31 (12.8)	*28 (77.8)*	*8 (22.2)*	
First seizure, type, n (%)				
focal seizures (intact awareness)	10 (21.7)			
focal seizures (impaired awareness)	11 (23.9)			
generalized tonic-clonic (onset unknown)	23 (50.0)			
generalized, non-motor (onset unknown)	0			
status epilepticus)	2 (4.4)			
incomplete file)	3			
Localization of BM (supratentorial *versus* infratentorial), n (%)				0.885[a]
single supratentorial BM)	28 (70.0)	*18 (64.3)*	*10 (35.7)*	
single infratentorial BM)	12 (30.0)	*8 (66.7)*	*4 (33.3)*	
Localization of BM (lobe), n (%)				
cerebellum	9 (22.5)	*6 (66.7)*	*3 (33.3)*	
brain stem	3 (7.5)	*2 (66.7)*	*1 (33.3)*	
frontal	16 (40.0)	*10 (62.5)*	*6 (37.5)*	
parietal	5 (12.5)	*3 (60.0)*	*2 (40.0)*	
occipital	2 (5.0)	*2 (100)*	*0 (0.0)*	
temporal	5 (12.5)	*3 (60.0)*	*2 (40.0)*	
multiple BM	202			
Depth of single supratentorial BM, n (%)				0.274[a]
subcortical or cortical	26 (92.9)	*16 (61.5)*	*10 (38.5)*	
white matter	2 (7.1)	*2 (100)*	*0 (0)*	
Tumoral hemorrhage on initial imaging, n (%)				**0.021[a]**
no	153 (64.3)	*129 (84.3)*	*24 (15.7)*	
yes	85 (35.7)	*61 (71.8)*	*24 (28.2)*	
file incomplete	*4*			

[+] The first column shows the respective characteristics, with main items in bold letters and sub-characters in normal letters. The second column shows overall values for all patients. Percentages for sub-items reflect their fractions. The third and fourth column show the fraction of patients

without and with seizures. Percentages refer to the fraction of patients with or without seizures for each item.

*Results of statistical testing, indicating p-values. Significant values are highlighted with bold letters, the respective statistical test is indicated with superscript letters: a, Chi square test; b, Mann-Whitney U test; Ref. = group of patients that served as a reference.

Table S3: Risk factors for pre-operative seizures[+].

	All patients with information on pre-operative seizures (n=554)	**No pre-operative seizures (n=471, 80.8%)**	**One or more pre-operative seizures (n=112, 19.2%)**	**p*=**
Sex, m/f	291/263	*228/217*	*63/46*	0.219[a]
Age, median (range)	61.4 (22.9-90.1)	*62.3 (22.9-90.1)*	*60.1 (31.7-84.9)*	0.160[b]
KPS, median (range)	80 (20-100)	*80 (30-100)*	*80 (20-100)*	0.319[b]
Number of BM, median (range)	1 (1-36)	*1 (1-36)*	*1 (1-20)*	0.433[b]
Primary tumor, n (%)				**0.037[a]**
unknown	39 (7.0)	*32 (82.1)*	*7 (17.9)*	0.895 [a]
lung cancer	222 (40.1)	*166 (74.8)*	*56 (25.2)*	**0.007[a]**
melanoma	90 (16.2)	*77 (85.6)*	*13 (14.4)*	0.159[a]
breast cancer	63 (11.4)	*59 (93.7)*	*4 (6.3)*	**0.005[a]**
renal cell cancer	23 (4.2)	*18 (78.3)*	*5 (21.7)*	0.892[a]
gastrointestinal	53 (9.6)	*41 (77.4)*	*12 (22.6)*	0.740 [a]
other	67 (11.6)	*52 (82.1)*	*12 (17.9)*	0.733[a]
First pre-operative seizure, type, n (%)				
focal seizures (intact awareness)	48 (44.4)			
focal seizures (impaired awareness)	6 (4.6)			
generalized tonic-clonic (onset unknown)	46 (42.6)			
generalized, non-motor (onset unknown)	6 (5.6)			
status epilepticus	3 (2.8)			
incomplete file	3			
Number of BM (n, %)				
single BM	238 (43.3)	188 (79.0)	50 (21.0)	Ref.
multiple BM	312 (56.7)	254 (81.4)	58 (18.6)	0.480 [a]
Incomplete file	4			
Location of BM (supratentorial *versus* infratentorial) (n, %)				
single supratentorial BM	199 (74.0)	*150 (75.4)*	*49 (24.6)*	**<0.001**
single infratentorial BM	70 (26.0)	*70 (100)*	*0 (0)*	Ref.
Localization of single supratentorial BM (n, %)				**0.026[a]**
frontal	94 (47.7)	*63 (66.3))*	*32 (33.7)*	**0.007[a]**
parietal	44 (22.3)	*34 (75.6)*	*11 (24.4)*	0.911[a]
occipital	25 (12.7)	*21 (84.0)*	*4 (16.0)*	0.297[a]
temporal	33 (16.8)	*31 (93.9)*	*2 (6.1)*	0.110[a]
Depth of single supratentorial BM (n, %)				
subcortical or cortical	174 (88.8)	*128 (73.6)*	*46 (26.4)*	0.075[a]
white matter	22 (11.2)	*20 (90.9)*	*2 (9.1)*	Ref.

[+]The results of subgroup of patients, who were operated, is shown. The first column depicts the respective characteristics item, with main items in bold letters and sub-items in normal letters. The second column shows overall values for all patients, values as indicated. Percentages for sub-

items reflect their fraction compared to the whole entity of a main item. The third and fourth column show the fraction of patients without and with seizures, marked with italic letters. Percentages refer to the fraction of patients with or without seizures for each item.

*Results of statistical testing, indicating p-values. Significant values are highlighted with bold letters, the respective statistical test is indicated with superscript letters: a, Chi square test; b, Mann-Whitney U test; Ref. = group of patients that served as a reference.